

ACTA MEDICA SCANDINAVICA

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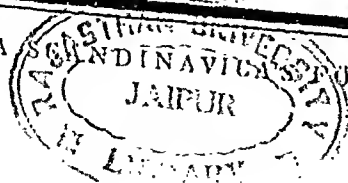
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From the State Bacteriologic Laboratory, Stockholm.

Investigations on Acute Infections of the Respiratory Tract.

IV. Experimental Studies on the Effect of Small Doses of Sulfonamides in Respiratory Tract Infections¹.

By

GUNNAR LÖFSTRÖM.

(Submitted for publication June 28, 1947.)

During World War II the combating of acute infections of the respiratory tract was regarded as one of the most vital tasks in military medicine. Intensive work was carried out in this field in England and U. S. A., in particular, and an exhaustive literature has appeared, the prophylactic aspect of the problem having been dealt with in some detail.

American and British research in this field has been organized on the lines of a comprehensive group research program. The American studies on the use of sulfonamides with a view to preventing acute respiratory tract infections and acute bacterial meningitis, as well as to stopping the appearance of complications, especially those following upon the primary virus infections, aroused great interest at the time of their publication. Attempts have also been made to lessen the incidence of rheumatic diseases in the same way. In the United States Navy, experiments (2) were in progress between December 1943 and April 1944, 250,000 men of military training age being involved in these tests. Special attention was paid to streptococcic infections, which were occurring in a particularly severe form in the early stages of these studies. From the results obtained, it was considered justifiable to draw the following conclusions.

¹ The expenses of this investigation were defrayed in part by a grant from Aktiebolaget Astra, Södertälje, Sweden.

with sulfadiazine. In recent investigations Hamburger et al. (6) have however tried to give small doses of sulfadiazine to dangerous carriers with promising results.

Studies on acute respiratory tract infections in military camps in Sweden have already been reported in earlier publications (Gard and Löfström (5), Löfström (8, 9)). The investigations described were in the main epidemiologic studies on acute infections of the respiratory tract, special attention having been paid to the causes underlying the occurrence of lobar pneumonia. In the first two publications, only the bacterial infections were studied, while the third took up the problem of the influenza virus for study and discussed the relation between virus infections and bacterial infections. Experimental studies on prophylactic and therapeutic treatment were also described. Thus, prophylactic vaccination against bacterial infections of the respiratory tract, mainly as a protection against lobar pneumonia, was described. Vaccine containing the pneumococcus and streptococcus types most commonly occurring in the infections under observation was used for these tests. No unequivocal results were obtained, however.

During the winter and spring months of 1939 an attempt was made to rationalize the indications for sulfonamide therapy among non-recumbent patients, using a material comprising 449 cases. This investigation resulted in certain guiding rules being set up for this type of treatment, these rules being discussed in some detail in one of the earlier publications (8).

The present article describes experimental studies on the effect of small doses of sulfadimin in acute respiratory tract infections, especially their effect on the course of the illness and the development of complications.

Material.

The investigation was carried out at the Svea Artillery Regiment in Stockholm, where all the persons examined were of military age and undergoing their military training. All men taken up on the sick list because of an acute respiratory tract infection during the period April 4 to June 11, 1945 were submitted to examination. The patients were divided into two groups. Every second man examined and taken up on the sick list for acute respiratory tract infection was given a tablet containing $1\frac{1}{2}$ g

of sulfadimin which he swallowed in the presence of the examining physician. At about 5 p. m., the same day, he was given, either at the hospital, if he had been admitted there, or when he returned for a second medical examination, another similar sulfadimin tablet which was also swallowed under surveillance. This was repeated daily until he was either remitted as cured or was moved away from the regiment. In the case of more serious bacterial complications the men were sent to the medical service of the Military Hospital or were started on the normal doses of sulfadimin at the camp hospital. In such cases it was a question of an unsuccessful attempt to prevent the occurrence of complications with the dosage of one gram a day.

Every other man in the series put on the sick list was used as a control.

In every case, on the day the men fell ill, a throat culture was obtained for bacteriologic study and a sample of blood was taken for serologic study. A second throat culture was made the day after, and again when occasion warranted it. Samples of blood were taken every ten days and were examined for complement-fixing antibodies against influenza A and influenza B virus.

One hundred and ten men were included in the investigation, after a number of cases had been excluded owing to the fact that they could not be followed satisfactorily. Some of the men included, however, had repeated infections unconnected with one another, with completely free periods in between, and the number of cases of illness therefore finally reached 130.

Fifty-eight patients were treated with $\frac{1}{2}$ g of sulfadimin twice daily (group A). The control group, B, consisted of 72 patients. In all other respects the treatment was identical in the two groups. Patients with acute respiratory infection and a subfebrile temperature were put on the sick list at the camp, those with a temperature of over 38° C were admitted to the camp hospital. Treatment with the full dose of sulfadimin for three days was instituted in the case of patients without localized complications in accordance with the following scheme.

- a. When the temperature was still over 38° C after three days' illness,
- b. When there were clinical signs of bronchitis and tracheitis,
- c. When the temperature rose again after an initial drop,
- d. When the temperature remained subfebrile for a long period in spite of rest in bed.

In the case of localized bacterial infections such as acute pneumonia, acute otitis or sinusitis, or signs of nephritis or polyarthritis, or when special tests or roentgen examination was considered necessary, the man was sent to the medical ward of the Military Hospital.

Symptomatic therapy against cough and pains was applied in the usual manner, but fever-reducing agents were not given.

Methods.

Bacteriologic technique.

Examination of throat cultures. Throat swab samples were taken from the tonsils and the posterior pharynx. The swab was transferred to one per cent glucose broth, and from this culture, after incubation in a thermostat for 6 hours at 37° C, a blood agar plate was spread and 1/2 ml was injected intraperitoneally into a white mouse. The blood agar plate and a culture from blood from the mouse's heart were examined for pneumococci, streptococci, and H. influenza. The pneumococci were typed by the Neufeld capsular swelling method. Streptococci producing soluble hemolysin were typed according to Griffith's type scheme in the manner described in connection with earlier investigations (8).

No attempts were made to detect influenza virus in the patients, as no cases of the influenza type were encountered.

Serologic examinations. All sera were examined for antibodies against influenza A and influenza B virus by means of the complement fixation test. The technique has been described in a previous publication (10). Attempts were not made to detect the presence of antibodies against the bacteria found.

Examination of the chemoresistance. The chemoresistance of the bacteria isolated was examined in the case of 51 pneumococcus and 48 streptococcus strains. These determinations were carried out by the method described by Smith (12). The bacteria were grown for 24 hours on 10 per cent horse serum broth. For the inoculation of the test tubes with different concentrations of sulfadimin, 0.1 ml of a 1/2,000 dilution, for pneumococci, and of a 1/20,000 dilution for streptococci was used. Broth was used for dilution. When the inoculum was examined by the plating method 2,000 to 20,000 bacteria were found in the case of the pneumococci and 500 to 5,000 in the case of the streptococci. The lower figure for the streptococci was used, as these bacteria showed a strikingly high chemoresistance to sulfadimin even when this small amount of bacteria was inoculated.

The sulfadimin, in a concentration of 40 mg per hundred millilitre, was dissolved in 0.3 per cent glucose broth. Further dilutions gave a series of tubes with 5 ml 10 per cent horse serum glucose broth in each tube containing as the largest dose 20 mg sulfadimin per hundred

ml. Successive halving of the doses brought the amount down to 0.02 mg sulfadimin per hundred ml in the eleventh tube. After the tubes had been inoculated with 0.1 ml of the diluted culture the series of tubes was incubated for 48 hours at 37° C. The sulfadimin concentration in the first tube giving a moderate to weak growth of bacteria was regarded as an expression of the chemoresistance of the bacterial strain.

Examination of the sulfadimin concentration in the blood. These determinations were made by Dr. R. Frisk on ten patients who were given the doses mentioned here, namely, $\frac{1}{2}$ g of sulfadimin morning and evening. The method used is described by Frisk (4).

Result of the Bacteriologic Examinations.

The bacteria found are shown in table 1.

Table 1.

Pneumococci and hemolytic streptococci isolated in cases of acute respiratory tract infection at the Svea Artillery Regiment during the spring of 1945.

P 1 = type 1 pneumococcus; SO = untypeable hemolytic streptococcus.

Bacterial type	Group A		Group B	
	One bacterial type in each case	Several bacterial types in each case	One bacterial type in each case	Several bacterial types in each case
P 1	2			
P 2	1	1		
P 3				2
P 4	1		2	1
P 5			1	
P 6	1	3	2	3
P 7	1	2	1	1
P 8		1	2	
P 9	1	2	6	2
P 10	1	1	2	1
P 11	2		3	3
P 12		1		
P 13	1	2	3	1
P 14	1			
P 15			3	
P 17		1	1	
P 18	1		1	
P 19	2			
P 20	1	2		1
P 28			1	
P 31	1			
P 32	1			
P 33		2		
P 34	1			
P 35	1			
P 41			1	1
S 30		10	9	8
SO	7		17	
Neg. finding	17			

As will be seen from the table, the different pneumococcal types and the hemolytic streptococci isolated occurred on the whole in about equal proportions in the two groups. A large number of pneumococcal types were represented but none of them caused an epidemic. No differentiation between the streptococcal types was obtained but there seems in any case to have been no question of an epidemic of streptococcal infections. In a large number of cases none of the mentioned bacterial species were encountered, a fact which may possibly indicate that a respiratory tract infection of the virus type was present.

Result of the Serologic Examinations.

Antibodies against influenza A and B virus were encountered to approximately the same extent as in a normal material. It can therefore be concluded that the infections in question were not influenza of any known type. No attempts were made to evaluate the etiologic significance of the bacteria present by means of antibody tests. Owing to the uniform nature of these bacteria it is unlikely that such tests would have furnished any valuable information. The bacteriologic examination was used here solely for the purpose of investigating the similarity between the two groups under treatment.

Result of the Investigation on the Chemoresistance of the Bacteria Isolated.

The results of the chemoresistance tests are shown in table 2.

Table 2.

In vitro tests on the resistance of various isolated strains to different concentrations of sulfadiminc.

Group	Bacteria	No.	Highest sulfadiminc concentration (in mg. per hundred ml.) permitting growth of bacteria on inoculation of 2,000 to 20,000 bacteria per 10 ml of serum broth.											
			>20	20	10	5	2.5	1.25	0.63	0.31	0.16	0.08	0.04	0.02
A	Pneumococci	23												
		22	8	1	2	2	4	3	10	2	4	3	2	
B	Pneumococci	28				2	1		7	8	7	1	2	
		26	8	2	3	3	3	2	3	1	1			

The table demonstrates that the pneumococci as a rule did not have a higher chemoresistance than 0.63 mg per hundred millilitres under these experimental conditions, while the streptococci were on a much higher level; a fourth of them even had a higher resistance than 20 mg per hundred ml.

Results of the Investigations on the Sulfadimin Concentration in the Blood.

The concentrations found are shown in table 3.

Table 3.

Concentration (in mg. per hundred ml.) of sulfadimin in blood with a dosage schema of $\frac{1}{2}$ g at 9 a. m. and 5 p. m. administered to patients of military age.

Patients	Concentration, in mg per hundred ml			
	on 2nd day of treatment		on 3rd day of treatment	
	9 a. m.	12 noon	9 a. m.	12 noon
1.....	0.5	0.8	0.6	1.1
2.....	0.6	0.9	0.6	1.0
3.....	1.0	1.5	1.4	1.7
4.....	0.4	0.8	1.5	1.2
5.....	0.6	1.4	1.1	2.0
6.....	0.7	1.3	1.0	1.5
7.....	0.4	0.8	1.4	2.0
8.....	0.7	1.0	1.0	1.0
9.....	0.6	1.4	0.8	0.9
10.....	1.0	1.2	0.8	0.9

The first sample of blood was taken before the first dose of the second day and the second sample three hours later. The values obtained show that this form of dosage gives a sulfadimine content which, at its lowest, ranges from 0.4 to 1 mg per hundred millilitres. The highest concentrations ranged from 0.8 to 2.0 mg per hundred ml.

Comparison Between Groups A and B.

Groups A and B were compared with respect to the number of days of illness and days in the hospital and also with respect to the appearance of complications. The results are shown in table 4.

The type of illness was uniform in the two groups. It took the form of catarrh of the throat, with or without coryza, and febrile catarrh. Typical cases of acute tonsillitis due to hemolytic strep-

Table 4.

Comparison between groups A and B with respect to the number of days of illness, days in the hospital and complicating diseases.

Groups	No. of cases	No. of days on sick list		No. of days at hospital		Complicating diseases				
		Total	Mean	Total	Mean	Acute pneumonia	Acute otitis	Acute sinusitis	Peritonsillitis	Other diseases
A	59	469	7.95	234	3.97	4	1			1 ¹ + 5 ²
B	71	512	7.21	230	3.24	2	1	1	2	2 ³ + 10 ⁴

¹ Acute polyarthrititis. (Patient given home leave.)

² Cases in which the full sulfonamido dose was instituted, in accordance with the indications mentioned in the text under Methods, or because of manifest bacterial complication. In group A, the four patients with pneumonia and one patient without localized complication were treated. In group B, two patients with pneumonia, three of those with other manifest bacterial complications, and five without localized complication were treated.

³ Two patients with acute lymphadenitis of the throat.

tococci occurred in about equal numbers in both groups. As to complications, acute pneumonia was the most serious. Of the four cases of acute pneumonia in group A, two were due to type 2 pneumococci and in two cases the cause was not ascertained. The two cases of pneumonia in group B were caused by type 1 and type 9 pneumococci, respectively. As regards the other complications hemolytic streptococci were the dominating factor.

From the therapeutic aspect, favourable results were not obtained from the use of small doses of sulfadimin. The number of days of illness and days in hospital were practically identical in both groups.

Discussion.

The investigation in question was carried out during a year which, from the epidemiologic standpoint, can be regarded as an intermediate year. No epidemics of respiratory tract infections of any importance occurred in that year, either of the influenza type or due to the epidemic occurrence of pneumococci or streptococci. This distinguishes this infection season from the previous one, when influenza A and an epidemic due to hemolytic streptococci occurred among the troops now under examination. It also distinguishes it from the following season, when an epidemic of

influenza B occurred. It is therefore quite evident that no therapeutic investigations covering one infection season only can hope to give completely unequivocal results. Such an investigation will contribute towards lessening the possibility of drawing conclusions from the results obtained, a task which is already difficult because of the relative smallness of the material. It would, however, already seem to be clear from these results that rather special conditions are necessary before similar attempts to shorten the course of the illness and to prevent the occurrence of complicating complaints by means of small doses of sulfonamides in acute respiratory tract infections, will have any prospects of therapeutic success. There would, however, hardly appear to be any danger of creating a set of chemoresistant strains as the result of experiments of this type with a short treatment time. Even now, the majority of the streptococcus strains displayed a surprisingly high resistance to sulfadimin, and there is therefore no reason for departing from the principle that sulfonamide compounds used for therapeutic purposes should be given in a full dose. The suggestions for the use of sulfonamide compounds in non-localized bacterial infections of the respiratory tract, which were advanced by the writer on the basis of investigations made during the winter and spring months of 1939, still seem to hold good.

The discussion on the use of small doses of sulfonamides is not to be regarded as closed in consequence of these findings. The first American experiments with prophylactic doses of sulfonamides were unsuccessful mainly, perhaps, because they were extended over a very long period. This resulted in cultivation of the chemoresistant strains but in all probability, this risk does not exist if this sulfonamide prophylaxis is used for a short period and for a definite purpose. Further experience is necessary before the final word can be said regarding the effectiveness of sulfonamide prophylaxis.

Summary.

A report is made on experiments with small doses of sulfadimin in acute respiratory tract infections, given with a view to shortening the course of the disease and preventing the appearance of complications. This form of treatment did not give the desired result. The use of sulfonamide compounds in full doses against

non-localized bacterial respiratory disease, and the possibility of preventing the spread of meningococcic and streptococcic epidemics with small doses of sulfonamides over short periods, are discussed.

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Some Clinical Problems Concerning Fatty Liver and Methylation Processes.

By

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(Submitted for publication August 4, 1947.)

Since the discovery of the ability of raw pancreatic tissue to prevent the formation of fatty liver in pancreatectomized animals, this and associated phenomena have attracted the attention of numerous workers. It is now realized that a whole series of factors plays a rôle in the development of that abnormality in fat metabolism which leads to an accumulation of fat in the liver cells.

The common view on the mechanism of fat transport in the organism is, that whether the fat is transported to the storage cells from the intestine or released from the depots for use in oxidation processes, a large part of it passes through the liver. This passage through the liver is in some way or other connected with the phospholipids, and if the latter substances are absent, or their formation is inhibited, the fat will be accumulated in the liver in the form of neutral fat or cholesterol esters. The phospholipid, the formation of which is often found impaired, is lecithine, but a reduced synthesis of cephaline is also capable of producing fatty liver. The limiting factor in the synthesis of lecithine is choline, and in the synthesis of cephaline it is inositol. It has also been found that the absence of certain fatty acids can give rise to fatty liver. Further the pancreatic hormone lipocaeic, and some other factors as well, play a rôle in these processes. Reviews of this field of research are to be found in recent volumes of *Ann. Rev. of Biochemistry*.

Without entering into a closer discussion of the various experimental methods of producing fatty liver, and of the theoretical

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problems thereby encountered, we should like to point out, that the most common cause of experimental fatty liver is a decrease in the amount of choline necessary for the synthesis of lecithine. It is probable that a reduced synthesis of lecithine plays a preponderant rôle in clinical problems of a similar type.

Choline is trimethyl-oxy-ethyl-ammonium-hydroxide. It occurs in normal food in lecithine, but can also be formed in the organism if labile methyl groups are present. However, these labile methyl groups cannot be synthesised in the animal organism, but must be obtained from without (from plants). By enzymatic transmethylation processes these methyl groups can be transferred to certain compounds which become methylated during the process. A deficiency of choline in the animal organism can be brought about by a decrease in the intake of choline or of labile methyl groups, or of both; further, an increase, on the part of the organism in question, in the demand for choline or labile methyl groups can clearly also lead to choline deficiency. In this connection it may be pointed out that the methyl groups of choline are also labile and can be transferred to suitable acceptors. This can, for instance, be seen from the fact that glycoeyamine, when given to rats can produce fatty liver in spite of the presence of otherwise sufficient amounts of choline in the food. The methyl groups of choline are transferred to glycoeyamine, the latter substance being thereby converted into creatine (19).

These problems acquired a particular interest for the clinician when it was shown that large quantities of choline when administered to rats, were able to prevent or reduce the toxic effect on the liver of carbon tetrachloride (2). It was also found that previous treatment of dogs with methionine, which under normal conditions is the most important donor of methyl groups, can protect the animals against the toxic effects of mepharsen (13). These results made the idea of treating cases of hepatitis and cirrhosis hepatis with choline or other compounds with labile methyl groups seem rather obvious, and some reports to this effect have already been given in the literature (10, 11, 14, 15, 16, 17, 21). Only in the treatment of hepatitis or cirrhosis combined with the presence of an enlarged liver was some slight effect observed. The treatment of real fatty liver was efficient. Simultaneous administration of choline and inositol is reported to exert a beneficial influence on cases of liver cirrhosis (12).

Since it would be of considerable value to be able to form an

estimate of whether patients with liver diseases (or other diseases as well) are deficient in labile methyl groups or choline, we have attempted to investigate whether the conversion of glycocyamine into creatine in such patients can furnish the basis of a test capable of deciding this question.

As already mentioned above glycocyamine is in the organism methylated to creatine by the transfer of methyl groups from choline, methionine or other compounds with labile methyl groups (9 and 18). Glycocyamine is the normal precursor of creatine, which, however, can be formed also in other ways (3). The synthesis of glycocyamine takes place in the kidneys, while the methylation process is associated with the liver and the muscles (6). The normal methyl donator is methionine (3).

Glycocyamine occurs in, for instance, brain, liver and muscle tissue. In greatest concentration (15—30 mg %) it is found in the kidneys (9). The daily urinary excretion in adults on a protein-free diet is 40—60 mg (9). The excretion is increased by the administration of arginine and glycine, both of which are used in the synthesis of the compound; glycocyamine can also be synthesised from glycine plus certain other substances (4). Glycocyamine is rapidly absorbed from the intestine and partly excreted in the urine (5). It is practically without any taste.

On administration of glycocyamine to man one might expect an increase in the content of creatine in the blood. This increase might presumably depend upon the store of labile methyl groups in the organism, or on its ability to effect a transmethylation reaction. This latter function might be expected to be reduced in cases of hepatitis.

Experimental Procedure.

In the morning the fasting subjects got 75 mg glycocyamine per kg body weight, and water ad libitum. Simultaneously the urine was collected and blood samples for the determination of creatine and creatinine in serum were drawn. In the following 5 hours blood samples were drawn every hour. Food was then given. The urine was collected and analysed for creatine, creatinine and methionine. The 24 hour urine in the days before and after the experiment was also analysed in the same way.

We have chosen to give the substance per os, since intravenous injections in man produced unpleasant symptoms (dyspnoea), perhaps as a consequence of impurities in our preparations.

Methods of Analysis.

Creatine and creatinine in serum and urine were determined according to A. Thomsen (20). On close examination this method proved fully satisfactory; added quantities of creatinine could be recovered completely both in serum and urine. The error of the method was less than $\pm 5\%$.

Methionine in urine was determined according to Albanese and coworkers (1). Added methionine could be determined quantitatively. It is, however, probable that also other substances than methionine are measured at the same time, since dilution of the urine decreases the amount of methionine determined more than corresponds to the degree of dilution; by dilution in the proportion 1:1 the amount of methionine is decreased ca. 15% less than corresponds to this dilution. Since the method involves an oxidation with such a powerful agent as perchloric acid, it is to be expected that other substances than methionine are also oxidised. However, larger changes in the excretion of methionine can undoubtedly be demonstrated by this method, which has therefore been used throughout the present work in spite of its inherent weakness. The method gives an error less than $\pm 5\%$ in the recovery of added methionine in urine.

Experimental Results.

We have studied 6 patients, 5 men and 1 woman, with hepatitis epidemica acuta. They were all in the acute phase of the disease with strongly increased serum bilirubine. Their age varied from 21 to 40 years. The course of the disease was typical and uncomplicated in 5 of the patients, and lasted from 1 to 2 months. One of them got chronic hepatitis.

In all patients the serum creatine increased during the experiment, while the serum creatinine remained unchanged. The average values are given in Table 1.

Table 1.

Serum creatine and creatinine in patients with hepatitis after administration of 75 mg glycocyamine per kg body weight. The values are expressed in mg %.

	At time of admin.	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
Creatine	1.02	1.75	2.35	2.78		
Creatinine	2.33	2.25	2.23	2.33	2.24 2.46	2.02 2.36

In 4 normal men of age 20 to 31 years, and in 2 patients (age 17 resp. 32) with asthma bronchiale a similar investigation was carried out, the results of which are summarized in Table 2.

Table 2.

Average values of serum creatine and creatinine in 6 normal subjects after administration of 75 mg glycocyamine per kg body weight. Values expressed in mg %.

	At time of admin.	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
Creatine	1.29	1.98	2.23	2.11	2.16	2.17
Creatinine	2.21	2.29	2.33	2.31	2.40	2.27

3 of the patients were treated for 45, 41 and 28 days respectively with 8 g of betaine hydrochloride daily. By this treatment the organism received labile methyl groups. The above experiment was then repeated. The average values of the results obtained before and after the treatment with betain are given in Tables 3 and 4.

Table 3.

Average values of serum creatine and creatinine in 3 patients with hepatitis before treatment with betain hydrochloride. Values expressed in mg %.

	At time of admin.	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
Creatine	1.01	1.90	2.23	2.51	1.92	1.60
Creatinine	2.32	2.25	2.28	2.13	2.38	2.29

Table 4.

Average values of serum creatine and creatinine in 3 patients with hepatitis after treatment with betain hydrochloride. Values expressed in mg %.

	At time of admin.	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
Creatine	0.91	1.29	1.36	1.56	1.53	1.40
Creatinine	2.76	2.74	2.75	2.63	2.72	2.70

Determination of Methionine, Creatine and Creatinine in Urine.

The daily excretion of methionine was determined in 6 patients with hepatitis epidemica. The variations from day to day are rather large, as can be seen from Table 5. The measurements covered a period of 7 days.

Table 5.

24-hours excretion of methionine in the urine of 6 patients with hepatitis.

Patient	Average	Extreme values
1.....	413	234— 789
2.....	470	131— 734
3.....	712	410—1 026
4.....	621	210—1 205
5.....	542	421— 616
6.....	464	206— 766

These values do not deviate from those obtained for normal subjects on ordinary diet. We further determined the excretion of methionine, creatine and creatinine in 3 patients 1 week before and 1 week after the treatment with betain hydrochloride was begun. In the 24 hour interval between these two periods the glycocyamine experiment and the analyses of urine mentioned above were carried out. The results are given in Table 6.

Table 6.

Average values of the 24 hours excretion of creatine, creatinine and methionine in the urine of 3 patients with hepatitis 1 week before and 1 week after the glycocyamine experiment, and on the day of the experiment.

	Creatine	Creatinine	Methionine
1 week before the experiment	0.29	1.32	632
Day of experiment	0.41	1.34	628
1 week after the experiment, during which betain hydrochloride is administered.....	0.28	1.41	572

The table shows that the excretion of methionine and creatinine is unchanged, while there is a marked increase in the excretion of creatine on the day of the experiment. Normal subjects showed an analogous behaviour.

Discussion.

It appears from Tables 1 and 2 that the administration of glycocyamine per os produces a marked increase in blood creatine, and that a somewhat greater increase is obtained in patients with hepatitis epidemica than in normal subjects. The difference is, however, small and is probably unimportant.

It is uncertain whether the observed increase in plasma creatine corresponds to an increase in the formation of creatine in the organism, since glycocyamine itself gives a faint red colour with picric acid. The intensities of the colours of creatine and glycocyamine are, under the conditions of our analyses and when the compounds are present in equal concentrations, approximately in the proportion 7 : 1.

However, if we assume that 75 mg glycocyamine per kg body weight are administered to a subject and uniformly distributed in the aqueous phase of the organism, the plasma concentration will be ca. 11 mg %, granted the further assumption that the aqueous phase amounts to $\frac{2}{3}$ of the body weight. In our analyses this would give a colour intensity corresponding to ca 1.5 mg %

creatine. However, such a uniform distribution of glycocyamine in the aqueous phase is unthinkable (on account of absorption and excretion). Moreover, the observed increase in plasma creatine in our experiments on hepatitis patients is greater than 1.5 mg %, namely 1.76 mg %. We must therefore conclude that a synthesis of creatine has taken place in the organism. The amount synthesised is probably small, since an analogous experiment with administration of creatine in stead of glycocyamine gives an increase in plasma creatine up to 13 mg % (20). A simultaneous determination of creatine and glycocyamine in plasma would give information about the magnitude of the creatine synthesis. In spite of numerous attempts the method of Borsook and Dubnoff (7) for the determination of glycocyamine in blood did not give satisfactory results, perhaps because the permutite accessible to us was unsuitable for the purpose.

However, on the basis of the results reported above, it can be definitely concluded that the investigation of the conversion of glycocyamine into creatine by means of serum analyses after administration of glycocyamine per os does not show any reduction in the ability of the organism to carry out methylation reactions in patients with hepatitis acuta compared to normal subjects. Likewise, this ability is not increased after treatment with betain hydrochloride (Tables 3 and 4). The observed increase of creatine in the urine on the day of the experiment is small and must be regarded as due to an excretion of glycocyamine. Both serum creatinine and urine creatinine were unaffected by administration of glycocyamine.

The content of methionine in the urine shows, by our method of analysis, no changes on administration of glycocyamine, and there is no difference between hepatitis patients and normal subjects. Since it is probable that in our analytical method the sulphur atom in the methionine molecule is oxidized, it is reasonable to assume that demethylated methionine (= homocysteine) is determined as methionine. Our investigations therefore do not give any information about the rôle of methionine in the methylation of glycocyamine or about its behaviour on administration of betain hydrochloride beyond the fact that the excretion of homocysteine + methionine remains unchanged.

Summary.

In an investigation of the ability of the human organism to convert glycocyamine into creatine by transmethylation processes no reliable differences have been found between patients with hepatitis acuta and normal subjects.

Further, the content of methionine in the urine remains unchanged in patients with hepatitis compared to normal subjects.

This investigation has been carried out with the support of Kong Christian d. X's Fond. I am glad to express my best thanks to Medicinalfabrikken Ferrosan A/S and to Prof. Dr. Stig Veibel for help with the synthesis of glycocyamine.

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Basal Metabolism in Subnutrition.

By

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(Submitted for publication June 27, 1947.)

During recent years, interest in the influence of protracted and severe subnutrition on the basal metabolism has gradually increased. In the clinic several cases of decrease in the metabolism due to nervous anorexia have thus been disclosed (Eggert Møller 1925; Bergman, 1930; Farquharson, 1938). Here the metabolism is from 10 to 30, more rarely up to 40 per cent below the normal standard.

Experimental investigations of the basal metabolism in cases of severe subnutrition have been published by Benedict (1915) and by Takahira (1925). In six fasting experiments of from 12 to 31 days' duration, which Takahira performed on male adults, the basal metabolism decreased from 10 to 32 per cent. The decrease did not commence before 3 or 4 days had elapsed, being greatest in the beginning, continuing all the time, however; it continued after the termination of the fasting period for up to 5 days, and then it was replaced by a rapid increase.

Many such investigations have been published. There are, however, but few which treat of the basal metabolism in cases of brief and slight subnutrition which are often met with in the medical clinic. In the available literature the writer has only found investigations by Eggert Møller (1931) and Forbech & Leegaard (1934), who have measured the metabolism of obese patients and found it unchanged after up to 5 months' reducing diet. In the following investigations the metabolism both of obese persons and of persons of normal weight was measured before and after brief periods of slight subnutrition. It must be of clinical

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importance to establish whether a change occurs under these conditions.

The basal metabolism was measured repeatedly on 18 patients and normal persons who had all been on normal diet before the commencement of the investigation. Two kinds of low-caloric diet were used, namely, an ulcer diet and a reducing diet, the caloric content of which, and in some cases also the protein content, were determined with the aid of Groth-Petersen's table. The reducing diet contained from 1,000 to 1,100 calories and from 50 to 60 g of protein. The caloric content of the ulcer diet to begin with was about 1,000 calories with about 55 g of protein, (1—1.5 liters of milk, 2 eggs, and 0.5—1.0 liter of oatmeal gruel) increasing gradually in the course of a week to normal values. In some cases it was ascertained that the diets were kept by controlling the nitrogen content of the urine.

In all the cases the basal metabolism was measured by the writer with the technique which is almost exclusively used in Scandinavia, that is to say, brief determinations of 10 minutes' duration with Krogh's apparatus on waking individuals who have been fasting for at least 12 hours, and who have been resting, in a waking condition, for at least half an hour. As normal standard was used Aub-Du Bois's standard as modified by Krogh, including Bjerring's figures for boys, and with determination of the surface according to Du Bois's formula: stature-weight. A respiratory quotient (R. Q.) of 0.82 was assumed. It may be a matter of opinion whether it is warrantable to employ a fixed respiratory quotient when the proportion between the fat and carbohydrate contents of the diet vary considerably — as it does in the ulcer diet given. On examination of one patient, the R. Q. before the ulcer cure was found to be about 0.82; at the beginning of the treatment it was 0.80, corresponding to a greater combustion of fat, rising at the end of the examination to about 0.90, corresponding thus to administration of plenty of carbohydrates. By employing an R. Q. of 0.82, when in reality it is 0.90, the metabolism is calculated too low by 1.8 per cent, but that is of no importance for the determination of the results, because the high respiratory quotient only occurs at a late stage of the cure.

The determinations of metabolism on the first day are unreliable, and they are therefore omitted in judging of the results. Douglas Robertson finds, however, that the measurements of the second day do not statistically differ from the subsequent deter-

minations, whence they have been regarded as being just as good. He likewise shows that the basal metabolism is measured just as reliably on out-patients as on patients who have spent the night in the hospital. On the other hand, it has not been found to be recorded in the literature whether confinement to bed in itself affects the basal metabolism in persons with normal metabolism. In order to answer this question it has only been possible to examine three patients who were confined to bed because of diseases which are not supposed to affect the basal metabolism (myoses, prurigo and osteo-arthritis). It was impossible to examine the normal basal metabolism before the confinement to bed, but this was done some time after the patient had got up. The following average values were found for measurings performed within 10 days prior to and within 10 days after the termination of the confinement to bed, namely, 100.4 per cent as against 102.8 per cent, 104.3 per cent as against 101.0 per cent, and 102.8 per cent as against 102.0 per cent. The average values were derived from 5 and 4, 3 and 3, and 5 and 4 measurings, respectively. The dispersion on the whole series of examinations was 3.6, 3.6 and 2.6 respectively. There was not found to be any influence from the confinement to bed, whence there was found no reason to distinguish between test subjects confined and those not confined to bed.

The investigations comprise 12 patients, 9 of whom were given ulcer diet, whereas 3 received reducing diet, and 6 normal persons, 4 of whom were given ulcer diet and 2 the reducing diet. The two groups differ essentially from each other, inasmuch as the normal subjects have been out of bed all the time, whereas the patients have been confined to bed most of the time. The normal subjects have thus performed a certain amount of work, which certainly has not been very great, the same diet therefore being less for them in proportion to their requirements. This does not, however, make any difference to the principle of subnutrition, namely, that it is brief and not very severe.

Looking at the results obtained for the 18 test subjects two cases are found which present very little dispersion of the determinations, at any rate, no change in the basal metabolism during the period of subnutrition. These are patient No. 9, on ulcer diet, and patient No. 14, on reducing diet. On the other hand, there are 12 cases in which a decrease is sure to occur, namely, in 7 patients and 2 normal test subjects on ulcer diet, and 2 patients

Table.

Basal Metabolism in 18 Persons under Brief and Moderate Subnutrition.

No. (a)	Normal metabolism (% of standard) (b)	Basal metabolism on 3'-7' days of subnutrition (% of standard) (c)	Difference (c minus b) (% of b) (d)
<i>Patients on ulcer diet:</i>			
1	99.0 (2)	94.0 (2)	- 5.1
2	101.3 (4)	97.5 (2)	- 3.7
3	104.3 (3)	96.5 (2)	- 7.5
4	101.5 (2)	97.5 (2)	- 3.9
5	109.5 (2)	101.0 (3)	- 7.8
6	101.7 (3)	95.7 (3)	- 5.9
7	100.5 (2)	99.5 (2)	- 1.0
8	90.3 (3)	85.5 (2)	- 5.3
9	98.3 (3)	98.0 (2)	- 0.3
<i>Normal subjects on ulcer diet:</i>			
10	100.0 (3)	98.7 (3)	- 1.3
11	103.0 (3)	97.3 (3)	- 5.7
12	103.3 (3)	98.5 (2)	- 4.8
13	101.5 (3)	93.0 (2)	- 8.4
<i>Obese patients on low-caloric diet:</i>			
14	96.0 (3)	95.5 (2)	- 0.5
15	94.7 (3)	87.0 (2)	- 8.1
16	103.3 (3)	99.0 (2)	- 4.2
<i>Normal subjects on low-caloric diet:</i>			
17	103.3 (3)	96.0 (2)	- 7.1
18 ..	97.7 (3)	94.0 (2)	- 3.8
Average			- 4.7 \pm 0.62

In columns b and c is parenthetically stated the number of basal metabolism determinations (on different days) giving the value.

and 1 normal test subject on reducing diet. In the remaining 4 cases the changes are doubtful. In the cases presenting a decrease in the metabolism, this amounts to from 5 to 15 per cent.

From the above-mentioned examinations of fasting basal metabolism it is seen that decrease and increase take place gradually, and that they do not occur until 3 or 4 days after the change of diet. Determinations performed on the first two mornings after the commencement of fasting may thus be used for determination of the normal metabolism. This circumstance has been taken advantage of in order to make a strictly objective evaluation

of the experiments, the normal metabolism being determined as the average of the determinations from 2 days before till 2 days after the commencement of the diet. Then during the treatment, in all the experiments the metabolism was determined as the average of the determinations made from the 3' to the 7' day, even though the diet was terminated a couple of days earlier. Then the results were compared and the dispersion computed, as may be seen from the table. The table shows that a decrease in the basal metabolism is found to occur from the third to the seventh day of subnutrition and that on an average it amounts to 4.7 per cent of the normal metabolism. The mean error for this result was calculated at 0.62 by computing the dispersion so that the changes in the basal metabolism are statistically certain and not a chance finding. The average decrease here determined does not, however, convey a reliable impression of the magnitude of the decrease, which, presented in a curve, may be found to be as high as 15 per cent.

It may thus be established with certainty that even a brief and moderate subnutrition, which will frequently be met with in the clinic, is able to influence the basal metabolism considerably, although this is not always the case. The decrease itself may become so considerable that it must be borne in mind when evaluating doubtful decreases in the metabolism.

Summary.

The basal metabolism was measured repeatedly in 18 patients and normal test subjects before and during brief and moderate low-caloric diets (ulcer diet and reducing diet). By statistical evaluation a decrease in the basal metabolism was found during the 3' to the 7' day of subnutrition, amounting to 4.7 per cent of the normal metabolism. The real range of magnitude of the decrease was 0—15 per cent read on curves which are omitted here. At the same time it was seen that decrease and increase commence after a period of latency of 3—4 days after the change of diet.

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Myocardial Infarction Resulting from Intravenous Administration of Hypertonic Solution of Sodium Chloride to Patients with Arteriosclerosis Obliterans of the Lower Extremities.

A Report on Three Cases.

By

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(Submitted for publication August 8, 1947.)

Allen, Barker and Hines (1), in their extensive review of peripheral vascular diseases, stated »the factors which produce arteriosclerosis obliterans of the lower extremities are likely to lead to similar lesions in other parts of the body; these appear frequently in one of the vital organs. The commonest of these lesions is coronary sclerosis with myocardial infarction. Less common is thrombosis of sclerotic cerebral arteries and still more rare is thrombosis of sclerotic mesenteric arteries.» In a series of 116 patients (Hines and Barker (3)) 54.6 % died within three years of their first visit to the Mayo Clinic. The majority died in a manner which was suggestive of, or actually due to, coronary occlusion. Other causes of death, besides coronary thrombosis, were cerebral vascular accidents, mesenteric thrombosis and bronchopneumonia.

Of the 25 patients with peripheral vascular sclerosis, and in whom the general condition was satisfactory enough to allow of a lumbar sympathectomy being performed, De Takats and his associates (2 a) found retinal sclerosis present in all, coronary sclerosis in 18, previous coronary occlusion in 2, nephrosclerosis in 5, hypertension in 10 and lipaemia (blood cholesterol over 250 mg %) in 3.

Thürlimann (4), in 1945, reported on the results of electrocardiographic investigation of a series of 138 patients suffering from »Endangiitis obliterans» (von Winiwarter-Buerger). Many of these cases, between 15 and 85 years of age, with an average age between 45 and 50 years, should probably be placed in the category of »arteriosclerosis obliterans», rather than in that of »endangiitis obliterans». Electrocardiographic evidence of serious myocardial damage was present in 38.4 % of these 138 patients, of whom 17.4 % had diffuse myocardial damage and 21 % electrocardiographic evidence of involvement of the coronary arteries, called by Thürlimann »coronaritis stenosans» and »coronaritis obliterans» respectively. In 9.5 % of the 138 cases in this series was myocardial infarction present. Even in young adults electrocardiographic evidence of serious myocardial damage was a not uncommon finding.

Our own material consisted of 18 patients, all men, treated for arteriosclerosis obliterans of the lower extremities. Their ages varied from 44 to 73 years, the average age being 54.7 years. In all cases the first visit to the hospital took place during the one-year period May 1946—May 1947.

Three of these patients developed myocardial infarction after the intravenous administration of hypertonic sodium chloride solution, and these will be discussed later. Two other patients, admitted on account of myocardial infarction in one instance combined with cerebral haemorrhage, had been suffering from arteriosclerosis obliterans of the lower extremities for some years. In 11 of the remaining 13 patients electrocardiograms were obtained, showing no abnormality in 6, slight but insignificant changes in 2, and evidence of serious diffuse myocardial damage in the other three. Electrocardiographic evidence of an insufficient coronary circulation was present in two of these three last cases.

If, therefore, in patients with arteriosclerosis obliterans of the lower limbs and who have been subjected to a particular method of treatment, myocardial infarction or cerebral vascular thrombosis develops during the course of treatment, there is usually no reason to suppose that the vascular accidents are due to those therapeutic measures. On the other hand, in the treatment of patients with arteriosclerosis obliterans it is advisable to omit all procedures which may favour the occurrence of vascular accidents in the heart and brain. The intravenous administration of hypertonic sodium chloride solution would appear to be one such procedure.

This method of treatment, originally used by Silbert (5 a, b, c) in patients with thromboangiitis obliterans (Buerger), was later employed by many investigators in the treatment of cases of arteriosclerosis obliterans as well. According to Silbert, and Samuels (6), a 2, 3 or 5 % solution of sodium chloride is used, Silbert usually employing 300 cc of a 5 % solution, containing 15 g NaCl. »The injections are first given three times a week, later twice a week, and the length of the intervals further increased as the patient improves; the fluid is allowed to run into the vein slowly during 10 minutes and the patient is kept flat on his back during this period» (Silbert, 5 a). There is much controversy regarding the value of this method of treatment, either in patients with thromboangiitis obliterans or arteriosclerosis obliterans, but this need not concern us here.

The rationale of this treatment has never been satisfactorily explained (Allen, Barker and Hines, 1). The current explanation, as offered by Silbert, is that the repeated intravenous administration of a hypertonic saline solution, by repeatedly increasing the blood-volume and thereby necessarily stretching the vascular system, is responsible for the improved circulation in the peripheral arteries and the development of the collateral blood supply. This favourable effect would last for some time.

If the injection is given too rapidly the patient may complain of headache, dizziness and an unpleasant feeling of warmth all over the body. Occasionally thrombosis occurs at the site of the injection (Allen, Barker and Hines). The patients often complain of thirst and in a few instances temporary jaundice occurred, resulting from blood destruction (Silbert). No dangerous reactions, and neither injury to the heart nor kidneys have been reported by Silbert (5 b) in more than 19,000 injections. Silbert, nevertheless, believes that this method of treatment is contraindicated in patients over 60 years of age and in those who show signs of myocardial damage or of poor renal function. Serious accidents or reactions resulting from this method of treatment have not, so far as we know, been reported in the literature.

Lequime and Denolin (7), however, reported in 1945 on circulatory disturbances following the intravenous injection of 40 cc of a 25 % solution of sodium chloride, containing 10 g of NaCl, into patients suffering from angina pectoris. According to these Belgian authors the intravenous injection of hypertonic sodium chloride solution brings about a considerable increase in the work

done by the heart, as evidenced particularly by the increase in the cardiac output and the acceleration of the circulation. Neither in normal persons, nor in patients with cardiac disease and normal coronary arteries, was this increase in the work done by the heart associated with electrocardiographic changes, whereas in patients with angina pectoris it produced marked electrocardiographic changes in the ST-segment, characteristic of acute coronary insufficiency. The method described was recommended by these Belgian authors as a test of heart function, to be used in place of the exercise-tolerance-test and anoxaemia-test.

From the investigations of these Belgian authors it may be concluded that in patients showing clinical evidence of coronary insufficiency and in patients with the latent form of this condition, the repeated intravenous administration (three times a week) of a hypertonic saline solution, containing from 10 to 15 g of sodium chloride, means nothing less than the repeated induction of a condition of acute coronary insufficiency of relatively long duration. The state of acute coronary insufficiency thus induced will persist longer than that caused by an exercise-tolerance-test or an anoxaemia-test. This procedure, in other words, is dangerous when carried out in all patients with hypertension, generalised arteriosclerosis, arteriosclerosis obliterans of the lower extremities, in all patients with evidence of an impaired coronary circulation and in all patients over 50 years of age. It should be remembered that slight disturbances in the coronary circulation are difficult to recognise.

Although, according to Allen, Barker and Hines (1), thromboangiitis obliterans (Buerger) cannot be considered to be a generalised or widespread vascular disease as such, the authors state that the visceral arteries of patients with thromboangiitis obliterans, especially the arteries of the brain and heart, likewise seem more than normally vulnerable to degenerative and thrombotic changes (Hausner, 8 a; Hausner and Allen, 8 b). The impending danger arising from intravenous infusion of hypertonic saline solution in cases of arteriosclerosis obliterans is demonstrated clearly by the following three clinical histories:

Case 1: A, a chauffeur, aged 53 years. For 5 years he had suffered from intermittent claudication, especially on the right side, but occasionally involving the left leg as well. After walking a few hundred metres pains arising in the right lower leg and calf forced him to stop. The pains disappeared after he had been standing still for a few minutes. He had a sensation of numbness and coldness in both feet. There was

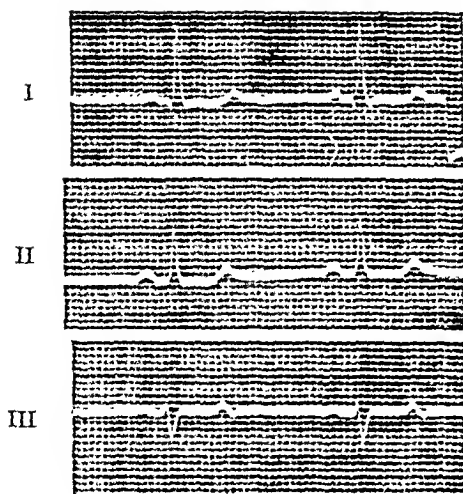


Fig. 1 a. October 15, 1946.

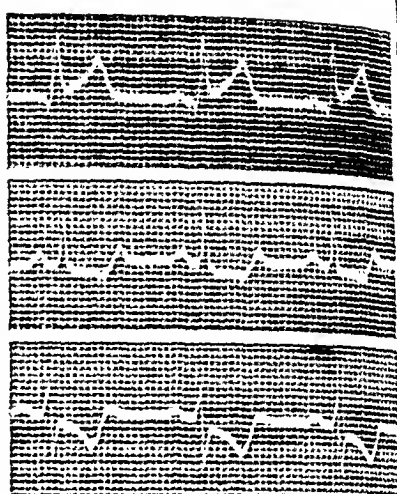


Fig. 1 b. December 6, 1946.

Fig. 1 (Case 1).

no complaint of shortness of breath, palpitation or precordial pain or oppression. He was a heavy smoker. Both parents had died from heart disease. At the first examination (October 15, 1946) heart and lungs appeared quite normal and clinical evidence of congestive cardiac failure was absent. Blood pressure: 195/95 to 190/90 mm Hg. Heart rate: 60 per minute. The skin of the right foot was pale and cold. Arterial pulsation in the left leg was unimpaired. On the right side, however, the femoral artery could be felt pulsating normally in the groin, but no pulsation was present in the popliteal, dorsalis pedis and posterior tibial arteries. Oscillometric examination using a Boullitte apparatus, with the cuff on the left calf revealed oscillations up to a maximum of 4.5 cm. (scale degrees), the normal maximum in this region being from 6 to 10 cm. Similar examination of the right calf showed the presence of oscillations up to a maximum of 1 cm.

Wassermann reaction: negative. Urine, urine sediment and renal function all normal. Haemoglobin: 85 %. Blood sedimentation rate: 5 and 13 mm after one and two hours respectively.

The electrocardiogram taken on Oct. 15 (Fig. 1 a) showed left axis deviation and flattening of the T-waves but no other abnormalities.

The patient was treated in the out-patient department with repeated intravenous infusion of from 200 to 250 ml of a 2 %, and later of a 5 %, solution of sodium chloride, given twice a week. The fluid was allowed to run slowly into the vein, taking 20 minutes during which the patient was made to lie flat on his back. On December 6 the 14th infusion was given. A few minutes after the infusion had been completed the patient suddenly noticed a severe precordial pain and a feeling of oppression in the region of his heart. Profuse sweating commenced and he was

compelled to lie down again. Blood pressure: 185/110 mm Hg. Heart rate: 100/minute. The heart sounds were soft and indistinct.

An electrocardiogram (Fig. 1 b), taken during the attack, showed a definitely elevated monophasic RST-segment in lead I and depression of the ST-segment in leads II and III, characteristic of a recent infarction of the anterior wall.

The patient was admitted to hospital. During the following days his temperature rose to 38.6° C (101.5° F), the white blood cell count increased to 20,000 per ml., while the blood pressure dropped to 120/90 mm Hg. In spite of repeated injections of morphine the precordial pain persisted. After a few days cardiac asthma and pulmonary oedema developed and death occurred on December 16. Postmortem examination was not performed.

Case 2: B, a clerk, aged 51 years. For five years he had complained of a feeling of tiredness and pain in the right leg and thigh while walking. For one year the same symptoms had been experienced in the left leg. These symptoms had increased in intensity during the past few months. After walking 100 metres severe pains in the legs had forced him to stop. Later a burning and throbbing pain developed in the feet and lower legs, especially when at rest and during the night. He had a sensation of coldness in both feet. There was no complaint of shortness of breath or of precordial oppression, even on exertion. The patient was a heavy smoker. He had lost a considerable amount of weight during the last year.

When first seen on May 2, 1946 the heart and lungs appeared normal on physical and radiological examination and there were no clinical signs of congestive heart failure. Blood pressure: 110/75 mm Hg. Heart rate: 68/minute. The skin of the feet was cold and blanched. Pulsation of the femoral artery in the groin was entirely absent on either side, as was pulsation of the popliteal, dorsalis pedis and posterior tibial arteries. Oscillometric examination of right and left calves showed no oscillation whatsoever. Wassermann reaction: negative. Urine: no abnormalities. Haemoglobin: 90 %. White blood cell count: 12,000/ml. Differential white cell count: normal. Blood sedimentation rate: 40 and 55 mm after one and two hours respectively. This elevation of the sedimentation rate persisted throughout the course of the disease. On May 8 and May 31 electrocardiographic records were made, showing on both occasions slight left axis deviation and low voltage QRS-complexes in the three standard leads. The ST-segments and the T-waves were quite normal (Fig. 2 a).

The patient was admitted to hospital. Intravenous administration of 250 cc of a 2 %, and later of a 5 %, solution of sodium chloride was started on June 7, and was repeated on June 12, 19, and 21, i.e. a total of four administrations. No reaction of any kind was noted on three occasions, but on June 12, however, the giving of the 2 % sodium chloride solution intravenously was followed after an interval of 15 minutes by a paroxysm of severe pains in the feet and lower legs on both sides, and the skin of the feet became blanched and cold due to

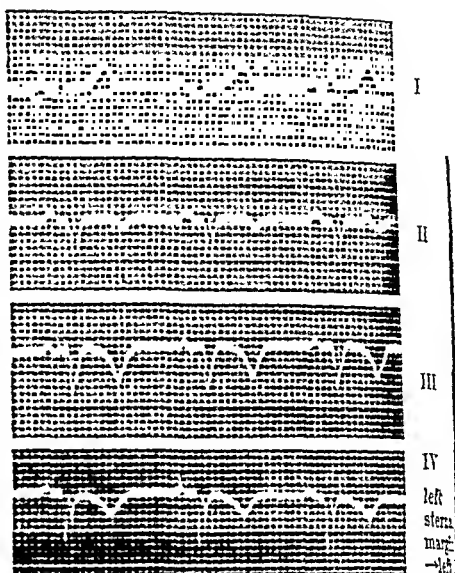
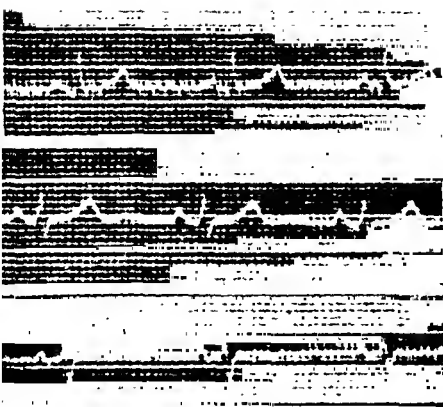


Fig. 2 a. May 31, 1946.

Fig. 2 b. June 22, 1946.

Fig. 2 (Case 2).

excessive vasoconstriction. The patient did not complain of precordial pain or precordial oppression. On June 22 an electrocardiogram showed considerable changes as compared with the record of May 31, exhibiting a QRST pattern in leads II and III characteristic of the subacute stage of a posterior infarct (Fig. 2 b). Clinical evidence of the development of the myocardial infarction had been absent, there having been no precordial distress, no elevation of the body temperature and no change in the already raised blood sedimentation rate. Physical and radiological examination of the heart revealed no abnormalities.

In this patient, the occurrence of spasm of the arteries in both lower legs following the intravenous infusion of 2 % solution of sodium chloride on June 12 indicates that a similar vascular reaction may have taken place in the coronary arteries, resulting in partial ischaemia and necrosis of the myocardium. After rest in bed for six weeks he was allowed up again. The electrocardiogram, characteristic of the subacute stage of a posterior infarct, remained practically unchanged during the following two months.

Case 3: C, a general labourer, aged 50 years, was first seen at the out-patient department on May 17, 1946, with the complaint that for four weeks he had had pains in the right leg while walking. He had been forced to stop after walking for 10 minutes and the pains had disappeared within a few minutes of standing still. The pains were dull and tiring in character and began in the right foot, subse-

quently spreading upwards to involve the calf, knee and thigh. He had a feeling of numbness and coldness in the right foot. There was also occasional complaint of palpitation, but shortness of breath and a feeling of oppression in the chest were completely absent. He was a heavy smoker. Examination of the heart and lungs revealed no abnormalities. Blood pressure: 145/85 and 140/85 mm Hg. Heart rate: 72/minute. The skin of the right foot was cold and moist, but was not discoloured. Pulsation of the femoral artery in the groin on the right side was hardly perceptible by the palpating finger; lower down the right leg arterial pulsation was absent. On the left side pulsation of the arteries was unimpaired except for the dorsalis pedis artery. Oscillometric examination with the cuff on the left calf showed normal oscillations up to a maximum of 5.5 cm (scale degrees) at a pressure of 110 mm Hg, whereas on the right side the oscillations were impaired, the maximum being 1 cm at a pressure of 110 mm Hg. Wassermann reaction: negative. Urine and urine sediment: normal. Haemoglobin: 95 %. Blood sedimentation rate: 4 and 15 mm in one and two hours respectively. Radiological examination of the chest showed the heart to be normal in size and configuration.

In the electrocardiogram of May 24 (Fig. 3 a) the P-waves in leads II and III were somewhat high, wide and pointed, and the T-waves flattened in all three standard leads.

The patient was treated with intravenous infusions of a 2 %, and later of a 5 %, solution of sodium chloride, given twice weekly. One month after the commencement of treatment the patient reported that the procedure had done him no good but had worsened his general health. Though his ability to walk had increased slightly, shortness of breath and a feeling of oppression in the chest and heart region had gradually developed since the beginning of treatment. These symptoms were attributed by the patient to the repeated intravenous infusion of hypertonic saline solution, and at his request treatment was temporarily stopped on June 26 after a total of nine administrations.

On July 29, while cycling, a paroxysm of violent precordial pain occurred, radiating to the right and left upper arms. He collapsed when he arrived home. The precordial pain persisted for some hours in spite of an injection of morphine.

On July 30 the patient was admitted to hospital. He was still weak and tired, but his general condition was satisfactory and the general examination revealed nothing of importance. Blood pressure: 180/110 mm Hg. Heart rate: 80/minute. Notwithstanding rest in bed paroxysms of precordial pain recurred on August 4 and 5, while on August 6 his temperature rose to 38.2° C (100.8° F), the blood pressure dropped to 115/85 mm Hg, and the blood sedimentation rate increased to 54 and 76 mm in one and two hours respectively, although the white blood cell count and the differential white count remained relatively unaltered. Everything considered, the complete clinical picture of myocardial infarction was present, and the accurate analysis of six serial electrocardiograms corroborated the diagnosis of a recent posterior wall infarct (Figs. 3 a and 3 e). Convalescence was uneventful.

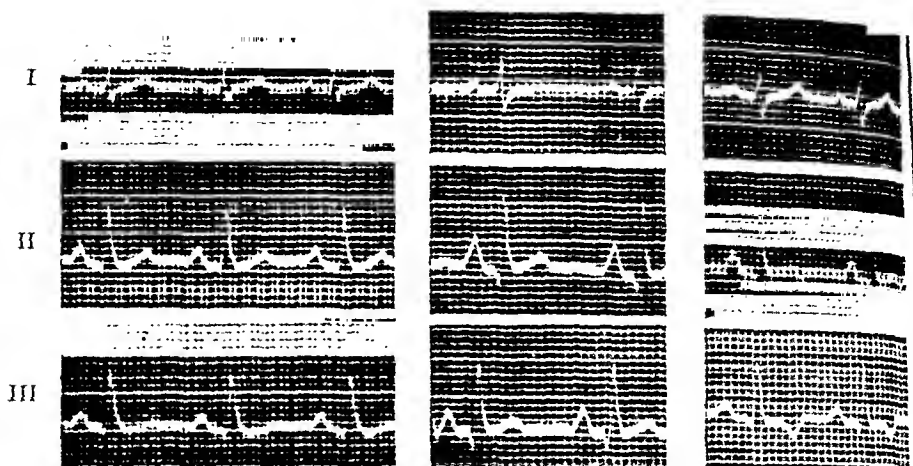


Fig. 3 a. May 24, 1946.

Fig. 3 b. Aug. 8, 1946.

Fig. 3 c. Aug. 29, 1946.

Fig. 3 (Case 3).

In this last patient, case III, treatment with repeated intravenous infusion of hypertonic saline solution cannot be considered to be the direct cause of the myocardial infarction as this developed more than one month after treatment had been terminated. Shortness of breath and precordial distress had, however, developed *during* the treatment, clearly indicating the possibility of a causal relationship between these subjective symptoms and the repeated intravenous infusion of hypertonic saline solution.

On account of the unfavourable results obtained in three of our own patients, and because of the convincing communication of Lequime and Denolin, we are justified in warning against the intravenous administration of hypertonic solution of sodium chloride to patients with arteriosclerosis of the lower extremities.

In those patients the use of an *isotonic* solution of sodium chloride, administered intravenously in a relatively short time, may also be dangerous. It is a well-known fact that in patients, in whom severe dehydration is present, *i.e.* severe *water and salt depletion*, the intravenous drip infusion of isotonic sodium chloride solution has proved to be of great value in overcoming the dehydration, and may be a life-saving measure. If the dehydration is extreme large quantities may be given in a relatively short time (9). In patients, on the other hand, *not suffering from water and salt depletion* and in whom sclerosis of the coronary arteries is present, the infusion intravenously of from 1 to 1½ litres of isotonic sodium

chloride in a relatively short period of time may result in acute coronary insufficiency as occurred following the injection of hypertonic solution in one case (case I), and probably in three of our patients, and also in the patients reported on by Lequime and Denolin (7).

The increase in the volume of the circulating blood is dependent on the total quantity of sodium chloride administered intravenously in a given space of time. The course of events may be briefly summarised as follows. The sodium chloride is distributed equally and almost instantaneously throughout all the extra-cellular fluid including the plasma. This results in an increase in the volume of the extra-cellular fluid, an increase in the plasma and total blood volumes and an increase in the work done by the heart together with the development of a state of »relative coronary insufficiency» proportional to the increased work done by the heart. Until the superfluous sodium chloride is excreted from the body by the kidneys the above-mentioned condition will persist, i.e. it will be of relatively long duration.

As is well known, the administration of sodium chloride or of sodium ions in large doses to patients with the latent form of congestive heart failure, whether orally, intravenously or subcutaneously, may be followed by the appearance of actual symptoms of this disease. The rapid administration of sodium chloride intravenously to patients with latent coronary insufficiency may, however, bring about a condition of »acute coronary insufficiency», and may eventually result in myocardial infarction.

Summary.

In three patients with arteriosclerosis obliterans of the lower extremities myocardial infarction developed, resulting directly or indirectly from the intravenous administration of a 5 % solution of sodium chloride. Causal relationship between the infusions of hypertonic saline and the subsequent myocardial infarction was undeniable in one case and strongly suggestive in the other two.

Treatment with repeated intravenous infusion of hypertonic sodium chloride solution is contraindicated, not only in patients with latent or actually existing congestive heart failure, but likewise in patients showing evidence of coronary disease, in arteriosclerotic or hypertensive patients and in all patients over 50 years of age.

In patients with the latent form of coronary insufficiency the rapid administration of sodium chloride intravenously can probably precipitate a state of acute coronary insufficiency, leading sometimes to myocardial infarction.

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Porphyrin in the Urine as a First Symptom of Leadpoisoning.

By

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When, about 20 years ago, the study of porphyrins in the clinic started, the presence of these mysterious substances was soon observed in the urine in cases of leadpoisoning. Since that time the presence of porphyrin is regarded as a regular diagnostic sign. The investigation of porphyrins is not yet so widely done in hospital and private practice as the more usual methods. This is somewhat surprising, as the method is a very simple one and the appearance of this substance in the urine is of great value in certain diseases, especially in leadpoisoning. Our examinations showed that porphyrinuria is the first sign pointing to the development of a leadpoisoning. The excretion of these substances appears far more regularly and considerably earlier than any other sign. Much earlier than for instance the basophile granulation of the red blood-corpuscles which in literature as a rule is considered as the first sign of leadpoisoning. Early diagnosis is necessary so that the necessary measures can be taken in time. This is all the more important, because lead is used in so many industries, and it is essential to protect the employers as effectively as possible. Also for the control of aqueducts and other water-supplies, of the use of special foodstuffs and in the Dutch East-Indies and other countries of East-Asia with the frequently used toilet-articles containing lead.

First some observations about the technique of the examination, such as we have applied and which in daily practice is most

simple. The definition is based on the fluorescent properties of coproporphyrin on radiation with ultraviolet rays led through a Wood's filter. It is not necessary to use an expensive apparatus, the simple and cheap lamp put on the market by Philips gives full satisfaction in practice.

The porphyrin which has the property to fluoresce red in ultraviolet light also occurs, but only in traces, in normal urine. The demonstration of this pigment in urine of healthy persons is therefore only possible, when one concentrates pretty large quantities.

Increased porphyrin-excretion in the urine is, when other causes, such as pernicious anaemia, haemolytic icterus, some feverish diseases, cachexy, idiopathic porphyrinuria and poisoning with various barburates are excluded, an important indication of leadpoisoning. With the aid of a semiquantitative estimation it is with some practice possible to judge whether the porphyrin-amount in the urine is normal, weak, moderate, strongly or very strongly increased. Even a weak, positive reaction must be regarded as a pathological sign.

If to 20 ml of urine some drops of glacial acetic acid and 2 ml of ether are added, and the test-tube is shaken to and fro some times, then in the ultraviolet light is seen that the layer of ether fluoresces:

- a) at normal porphyrin-concentration light blue to light green.
- b) at slight increase just observable red fluorescence.
- c) at moderate increase distinct red fluorescence.
- d) at strong increase strong red fluorescence.
- e) at very strong increase a still stronger red fluorescence.

Moreover in these cases the porphyrin can be demonstrated spectroscopically, but this requires more practice.

For this simple investigation we render the observations in ultraviolet light consecutively with:

- a. —
- b. +
- c. ++
- d. +++
- e. ++++

This semi-quantitative method is a very useful guide. If the result is equivocal or when a more accurate determination is required, the porphyrin can be estimated quantitatively.

For this examination one needs the full 24 hours' urine. The urine should be examined fresh, if this is impossible it may be preserved by the addition of a few crystals of thymol and stored in a cool dark place, as porphyrin is decomposed by light. 10 ml of a 24 hourly specimen of urine, preserved as above, are acidified by the addition of 5 ml of glacial acetic acid. 10 ml of ether is added and the mixture shaken. The porphyrin content is readily absorbed by the ether from an acid medium. 2 or 3 ml of water are added to remove extraneous pigments and the excess of acetic acid. The porphyrin is next extracted from the ether by four shakings with 5 % muriatic acid, about 3 ml on each occasion. In most cases the muriatic extract is suitable for the quantitative determination of coproporphyrin. Now and then the difficulty occurs that the muriatic acid carries with it various pigments from the urine. As a result of this the muriatic extract does not fluoresce purely red in ultraviolet light. By shaking out with benzine and carbontetrachloride however these disturbing substances may be easily removed. The quantitative analysis now takes place in the ultraviolet light with the help of a simple colorimeter, as was formerly amply described by Hijmans van den Bergh and Grotepass (1). As a standard, solutions are used of coproporphyrin in 5 % of muriatic acid, which contain in declining concentration 10, 7, 5, 3, 2, 1 and 0.7 gamma of this pigment. In normal urine samples in general values are found from 5 to 20 units. Values between 20 and 30 units indicate a possibility of lead-intoxication. Values above 30 units are to be considered as definitely pathological.

In the semi-quantitative method first described, mistakes can be made which are excluded with the quantitative method. False results may especially occur in the weaker concentrations in the urine, because the determination takes place without further purification of the ether-extract. Therefore it is possible that a weak fluorescence can be weakened by admixed substances of unknown origin which give in ultraviolet light a blue to greenish blue fluorescence. So one may sometimes find a urine negative which in reality might prove to be still slightly positive after purification of the ether-extract. Or a weak reaction is found, where this should have been in fact strong or moderate. So mistakes can be made by declaring urines negative which in reality are still positive. But the reverse that a positive reaction is found where there is nothing in reality, fortunately never occurs. This

renders a positive, reliable background to the conclusions which may be derived.

In our hospital hundreds of urine samples were examined of persons who had not been in special touch with lead; the simple semi-quantitative method always gave a negative result.

That the porphyrin can appear in the urine early in leadpoisoning is also mentioned by Vannotti (2). He says that porphyrinuria can often appear already before any other symptom of leadpoisoning is present.

In the publications about mass-examinations mention is only made about the appearance of basophile granulation. It is then pointed out that the basophile granulation may be considered as an early sign of chronic leadintoxication, while it is also found at the acute attacks. It need not occur, however, in either of the two conditions. Some found the basophile granulation to decrease again when the symptoms of leadintoxication increased. Usually the basophile granulation disappears soon after recovery of intoxication; however it may continue sometimes for more than a year.

In an extensive investigation, by one (3) of us in the centre of the province of Limburg, into the occurrence of leadpoisoning as a result of leadecontaining water, the author found that the appearance of porphyrin in the urine was a more constant and earlier sign than the basophilic stippling of the erythrocytes. We consider a basophilic stippling as abnormal, according to what generally is accepted in literature when the numbers are higher than 1 ‰. That is why we used the determination of porphyrin in urine as a guide diagnostic test in a mass determination in 800 persons, controlling simultaneously the leadecontents of their drinking water.

At the same time it is a great advantage that this test is an easy one, takes only a short time and avoids technical errors as well as the influence of fatigue which cause inaccuracies in the counting of the basophilic red cells.

To compare both symptoms and their relative value as a diagnostic test we made a second research two months afterwards. We controlled 87 persons of the same group who previously showed a +, ++, +++ or more than +++ porphyrin in their urine. This time we made a comparison of both tests.

Comparing the results obtained in both series of urine examinations we see that in 22 cases the strength of the reaction has

remained equal, in 41 cases the porphyrin-reaction has become weaker, sometimes even considerably weaker; in 12 cases it has even gone from ++ or stronger quite negative now, in 20 cases the reaction has become stronger. For the change in the porphyrin-excretion different explanations may be given.

Firstly it is possible that they may be explained as mistakes in the technique.

Secondly it is possible that the porphyrin-excretion just as the lead-excretion is liable to fluctuations; they may go parallel. In order to control this one should have to examine the 24 hours urine samples for a longer time.

Thirdly the cause may be found in more or less waterconsumption, but also in fluctuations of the lead-percentage of the water. It is very possible that all these causes have some influence. If we take for instance the cases where the porphyrinuria has decreased, the first examination was made in the hot summermonths, in which the water-consumption is generally considerable. Moreover then the water is warmer and more lead may be dissolved in the water from the pipes. The appearance of a family-diminution of the porphyrin-excretion supports this conception in many cases.

In the next table we show the result of the comparison between the increase of the number of basophilic erythrocytes and the amount of porphyrin in the urine.

Table.

Porphyrin	Basophile granulation	Number of persons
—	0 ‰	9
—	1 ‰	1
—	2 ‰	2
+	0 ‰	13
+	1 ‰	6
+	2 ‰	5
++ or more	0 ‰	28
++ or more	1 ‰	9
++ or more	2 ‰	12
either unknown		2

From this investigation it appears clearly that in certain cases a clearly pathological porphyrin-excretion coincides with simultaneously 0 ‰ basophile granulated erythrocytes. In only two cases a basophile granulation of 2 ‰ exists with a negative

porphyrin-reaction of the urine, but both cases had a +++ reaction at the first examination. So it is possible that the basophilic granulation has decreased more slowly than the porphyrinuria or has continued longer.

As a further test we persuaded some normal persons to take a quantity of water containing lead acid daily for a long period. For this some assistants, students and nurses put themselves voluntarily at our disposal.

At the first examination the volunteers were divided into four groups which each took $\frac{1}{3}$, $\frac{2}{3}$, 1 or 2 mg of lead first thing in the morning. Regular testing showed that the consumers of 1 or 2 mg a day had a clear pathologically increased porphyrin-excretion in the urine after $2\frac{1}{2}$ and 1 month respectively, while the basophilic granulation was still 0 ‰. Of the consumers of $\frac{2}{3}$ mg a day the urine contained likewise a clearly increased amount of porphyrin after about $3\frac{1}{2}$ months; also in these cases the basophilic granulation remained 0 ‰. Finally of those who used $\frac{1}{3}$ mg a day; after 7 months the porphyrin-excretion had still remained normal and the basophilic granulation 0 ‰. In the other cases after finding definitely pathological porphyrinuria, the administration of the water containing lead-acid was stopped and consequently not continued, until the appearance of basophilic granulation especially also, because in the groups taking 2 and 1 mg the volunteers sometimes complained of feeling ill, poor appetite, insomnia etc.

Afterwards one of us¹ has repeated the same experiments with some variations. To two healthy persons three times a day $\frac{1}{3}$ mg of lead was given during meals. This in contrast with the previous series, where the lead, dissolved in some water was always used in the morning before breakfast. To two other persons twice a day at lunch and at dinner $\frac{1}{3}$ mg of lead was administered. While he found in the first experimental series that after the use of 1 mg the porphyrin in the urine became positive after about $2\frac{1}{2}$ months, the porphyrinuria of our two persons using lead during the meals, appeared after resp. $4\frac{1}{2}$ and $5\frac{1}{2}$ months. With $\frac{1}{3}$ mg, twice a day given at meals, in one patient the reaction was positive after more than 6 months. The second volunteer stopped taking it at the same time and the reaction was still negative.

¹ C. D. de L.

So we see that when the water containing lead is divided over the day and is used with meals, a larger dose or a protracted use is necessary before a distinct porphyrinuria appears.

With none of the four experiment-persons an increasing basophile granulation was found.

Next we tried effect of more prolonged administration. One volunteer took 2 mg of lead every morning before breakfast. On the 25th day the porphyrin-reaction was clearly positive. He continued to use the lead till the fiftieth day. The porphyrin was now very strongly positive. We thought it safer to stop the experiment for the present, though, except for a slight fatigue, no other subjective or objective symptoms had occurred. Basophile granulations had not appeared. We continued to follow the further progress after ceasing the administration. After 2 months the porphyrinuria had disappeared again, basophile granulation was not found. The volunteer took lead again in the same quantity and in the same way as at first. After a week the reaction became clearly positive again, but no basophile granulation. After the appearance of the porphyrin the taking of lead was continued for a further two weeks. For reasons of caution we stopped then, not because special symptoms appeared. The porphyrinuria was again strong, the basophile granulation failed to be shown. Again the porphyrinuria disappeared gradually, and after five weeks was almost negative. Again a lead-free period of two months was instituted, then again the administration was restarted. Now the porphyrin was clearly positive on the 6th day, but also now the granulation-test failed. Again we went on for two weeks and then stopped for two months. After that we began again with lead, already on the 4th day porphyrin was present. Ten days later the basophile-granulation was observed for the first time, viz. 3 ‰. The experiment was stopped then. Owing to the fact that one of us had to stay in a concentration camp, there was no opportunity to follow the further process. Only after ten months we were able to make any further observations. Then both porphyrinuria and basophile granulation had disappeared. Our volunteer felt quite normal and absolutely no abnormal signs were to be found.

We have done the same with a second person. In the third period when the lead was taken, no basophile granulation had yet appeared, on the other hand there was a strong porphyrin-excretion. Again the occupiers of our country caused the examination to be stopped prematurely.

These investigations indeed point out that porphyrinuria determination is much more important than a basophile granulation-test.

For a routine-control of workers in the lead-using industries, the semi-quantitative porphyrin-method is much better than looking for a basophile granulation. Not only because the sign appears much earlier, but also because the technique is more simple and reliable. The same holds good for the control of aqueducts and in other circumstances, where one wishes to ascertain if the lead is absorbed by man in a relatively too large quantity. It stands to reason that also for examining individual cases, estimation of porphyrin must be considered as an important diagnostic test.

Summary.

A description is given of a simple semi-quantitative method of estimating porphyrin in the urine.

Based on details obtained in an extensive investigation of symptoms of lead-poisoning in the population of a district where the water was highly lead-containing this method appeared to be more reliable and to provide a more constant diagnostic test for detecting the first signs of lead-poisoning than the basophile granulation of the erythrocytes.

This was proved (1) by a comparative examination of both criteria with 87 persons who all had a more or less high porphyrin-excretion due to lead and (2) by an experimental examination of normal persons taking predetermined quantities of lead.

The method is recommended for the examination of large groups of persons who are regularly exposed to contact with lead, such as workmen in some industries etc.

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Copenhagen,

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the Institute for General Pathology, the University, Copenhagen,
Director: Professor K. A. Jensen, M. D.

Resorption of Penicillin after Inhalation.¹

By

POUL DRAGSTED and MICHAEL SCHWARTZ.²

(Submitted for publication August 4, 1947.)

Introduction.

In the course of time inhalation of a great variety of substances has been used for local treatment of diseases of the lung. Apart from the excellent symptomatic effect of Epinephrine by attacks of asthma, the drugs used have hardly had any beneficial effect worth mentioning.

On the appearance of the sulfonamides attempts have been made to use these efficacious drugs, partly locally towards infectious pulmonary diseases (10, 19, 21), partly attempts have been made to have the substances resorbed into the blood-system after inhalation (21). In order to obtain reasonable blood-levels it is, however, necessary to nebulize heavily concentrated solutions, and few sulfonamides only are sufficiently soluble. As, furthermore, the sulfonamides are fully efficacious per os and must not be overdosed, this method for general sulfonamide-treatment is of no great interest.

Penicillin, on the other hand, is easily soluble, quite harmless, and rather inefficacious given per os — a substance which might seem well qualified for local treatment of infections of the respiratory organs. Also would it be of interest to examine the possibility of having the drug resorbed into the blood-system after inhalation, to avoid, if possible, the many injections which are otherwise necessary in penicillin-treatment.

¹ The penicillin-assays of the blood have been aided by a grant from Miss P. A. Brandt's foundation.

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Treatment of Pulmonary Diseases with Penicillin-Inhalation.

In 1944 Bryson et al. (8) proposed the use of penicillin for local treatment of infections in the respiratory tracts. The first investigations on this treatment appeared in 1945, when Barach et al. (3) reported favourable results with penicillin-inhalation-treatment of bronchiectasia, lung-abscesses, and chronic bronchitis. Later on several reports have appeared about the results of this treatment, among others Hampton et al. (12), Abramson (1), Segal & Ryder (28), Vermilye (32), Morse (20), Olsen (23) from U. S. A., Southwell (29) and Humphrey & Joules (14) from England, Geiser et al. (11) from Switzerland, Linde (18) in Sweden, and several others.

The results have, generally speaking, been most encouraging, especially as far as the treatment of lung-abscesses, bronchiectasia, and chronic bronchitis is concerned. The general condition improves quickly, the quantity of the expectoration declines, the penicillin-sensitive bacteria disappear from the expectoration. Most cases of lung-abscesses are said to be cured this way, and many cases of bronchiectasia are made better qualified for surgical therapy. Pneumonias also can be treated exclusively by penicillin-inhalation, just as the treatment is recommended by acute bronchitis, sinusitis (4, 6), lung-stasis, and preoperatively by diseases of the lung to prevent complications (bronchial fistulae) (29).

The pathogenic bacteria in question are especially pneumococci, streptococci, and staphylococci, of which most strains are penicillin-sensitive. A possible complication by a successful elimination of these bacteria in the respiratory tract is secondary growth of penicillin-resistant bacteria, here particularly coli (14, 29). To a certain degree this complication can be prevented by intermittent or final sulfonamide-treatment. Streptomycin has also been used for this purpose, and apparently with good results (24, 25).

Even if indications and dosage for penicillin-inhalation-treatment of diseases in the respiratory organs have not yet been laid down, this treatment will probably by degrees win great extension, since it is logical and simple; just as in wound-treatment the penicillin is applied directly to the infected area.

Resorption of Penicillin after Inhalation.

Earlier Examinations.

There are only few reports in literature concerning the penicillin-resorption from the respiratory organ into the blood. Most examinations on the penicillin-levels in the blood after inhalation have been performed as single determinations in patients being treated for pulmonary diseases, and are not very instructive. Still it is agreed that after inhalation of 25,000 i. u. one can shortly afterwards obtain therapeutic concentrations (2—10 i. u. per 100 ml) (4, 11, 14, 15, 16, 28, 30).

Mutch & Rewell (22) in England and Segal & Ryder (28) in U. S. A. investigated the penicillin-blood-levels after inhalation at a few normal volunteers. Mutch & Rewell found considerably varying values several of which were very high compared with other examinations (averagely 3.5—4.0 i. u./ml serum after inhalation of 155,000—328,000 i. u.). The experiments — 5 in all — allow no concrete conclusions.

Own Examinations.

At the Medical Out-Patients' Department, Rigshospitalet, we have performed a series of examinations concerning the resorption of penicillin after inhalation.

The purpose of the examination has been:

1) to examine which penicillin-blood-levels it is possible to obtain after inhalation of varying quantities of penicillin.

2) to examine how modifications of the technique influence the resorption, including especially the efficiency of various nebulizers.

Method.

Healthy undergraduates and nurses have been used for the investigations. The penicillin has partly been American (Lederle), partly British (BDD). The penicillin is dissolved in physiological saline in such a way as to make the quantity of the liquid 1—3½ ml. To decrease the loss in the nebulizer ½ ml saline is finally atomized. The American Vaponephrin-nebulizer has been used for these experiments, the pressure for nebulization being delivered from an oxygen cylinder. The volunteers have inhaled until the nebulizer was emptied, which would last from 7 to 30 minutes, dependent on the quantity of the liquid. Between the oxygen

cylinder and the nebulizer a T-tube is inserted; during the inspiration a finger is placed at the open end of the tube so as to make the nebulizer work during the inspiration only. The volunteers have been instructed to breathe deeply, but otherwise regulate the speed themselves. The nebulizer is extended by a short, thick T-tube, upon which a 4 l rebreathing bag is placed with 3–400 ml water 104° F. at the bottom. The volunteer inhales through the open end of the tube, held in the mouth.

The quantity of penicillin in the blood is determined at various times after the inhalation, the first determination being made immediately after the end of the inhalation. The blood samples have been placed in the ice-box at once, centrifugated a few hours later, and after off-pipetting of serum the penicillin-contents have been assayed according to the serial-dilution-method at the Institute for General Pathology (33).

Penicillin-Blood-Levels.

After inhalation of various quantities of penicillin we have found the blood-levels seen in fig. 1–6.

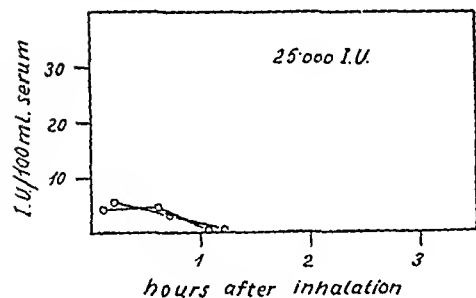


Fig. 1.

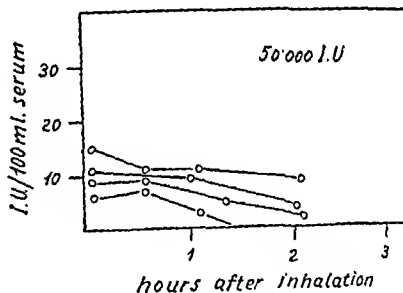


Fig 2.

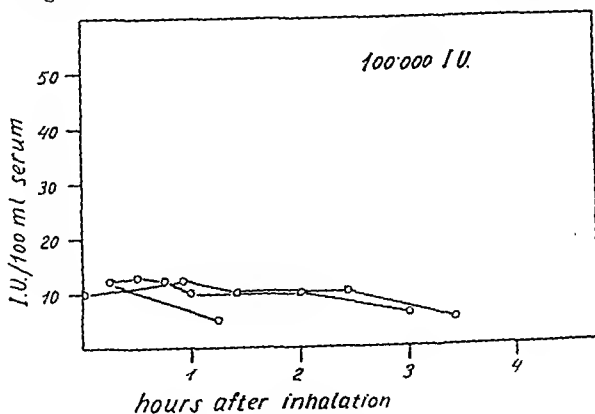


Fig. 3.

RESORPTION OF PENICILLIN.

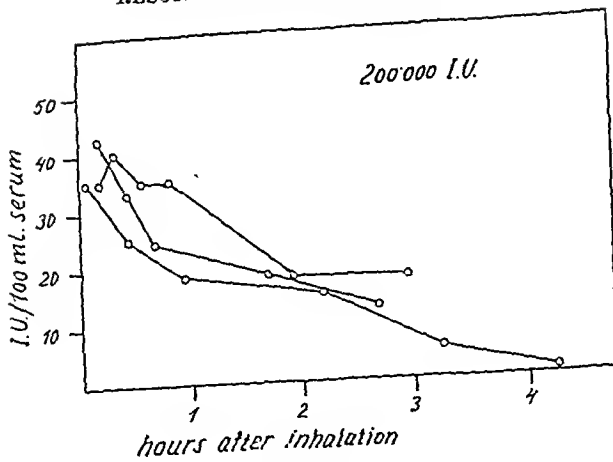


Fig. 4.

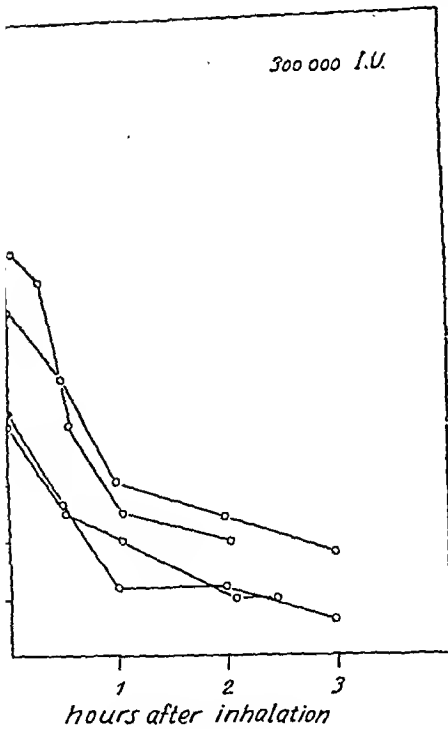


Fig. 5.

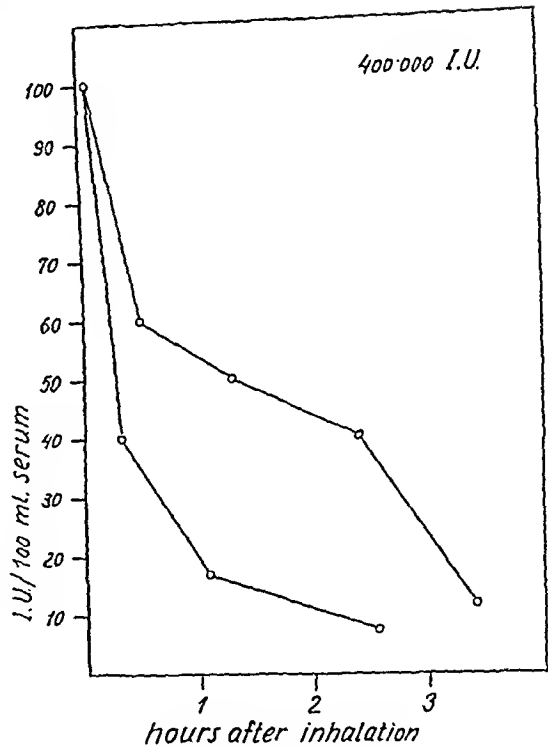


Fig. 6.

Fig. 1—6. Penicillin blood levels following the inhalation of penicillin aerosol (25,000—400,000 i. u.).

By way of comparison it is shown how the curve is after intramuscular injection of 40,000 i. u. (fig. 7).

It appears from these curves that it is possible by inhalation to obtain even high penicillin-blood-levels, but also that this form of administration must be expensive.

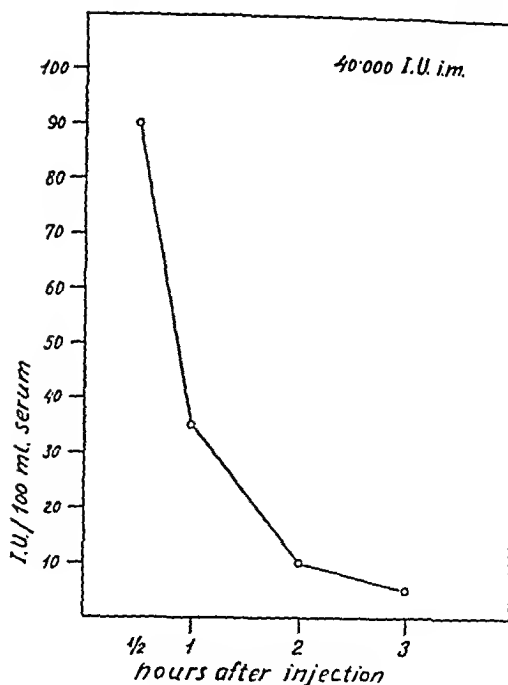


Fig. 7. Penicillin blood levels following intramuscular injection (40,000 i. u.)

There is quite a lot of difference in the concentrations obtained by various persons; counting on a medium resorption, about $1/6$ — $1/7$ only of the atomized quantity of penicillin will be found again in the blood. These results correspond to what Segal & Ryder (28) have been able to find — still apart from Mutch & Rewell (22) — who find resorption of about $1/4$ of the atomized quantity.

From the course of the curve it appears that the penicillin-concentration rises to its maximal value at once, almost as quickly as after intravenous administration. The curve may decline a little more slowly than after intravenous and intramuscular administration, but apparently there is no great difference.

In some experiments we have followed the blood-levels after repeated inhalations.

As expected you can easily maintain the concentration in the same way as by intramuscular administration; there seems to be no cumulation (fig. 8).

In different ways we have tried to vary the technique to explain the great loss of penicillin.

1) The value of the rebreathing bag is doubtful, we have not

RESORPTION OF PENICILLIN.

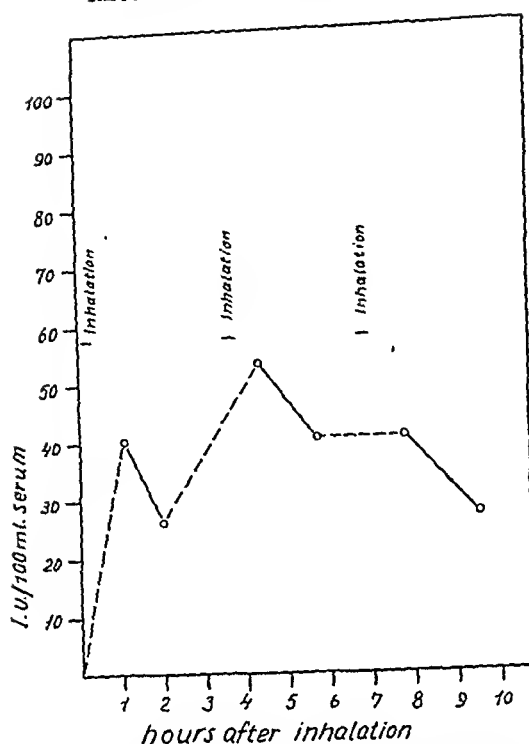


Fig. 8. Penicillin blood levels following the repeated inhalation of 200,000 i. u. penicillin aerosol every 3 hours.

found any definite difference by excluding it — by one person even a little higher values — and we can accordingly confirm Abramson's (2) opinion on the importance of the rebreathing bag.

2) Instead of leading the tube directly into the mouth we have tried to use a face-mask with inspiration and expiration valves. This will clearly increase the loss of penicillin — the penicillin sticks in the valves —, and the penicillin-values are half as high only when using the mask (fig. 9).

3) By the application of a thick glass S-tube in extension of the mouth of the nebulizer we have tried to catch greater drops which possibly leave the nebulizer, and which will never get to the lungs. Towards the end of the inhalation the tube has been rinsed with a little saline, which was then nebulized. By this modification we have not obtained any greater resorption.

4) We have tried to add glycerin in 20 % to the penicillin-solution; this makes the nebula steadier, and Prigal (26) has maintained that the resorption will increase at such a stabilization, as yet no results have, however, been published. In a series of experiments the same volunteers have received the same quan-

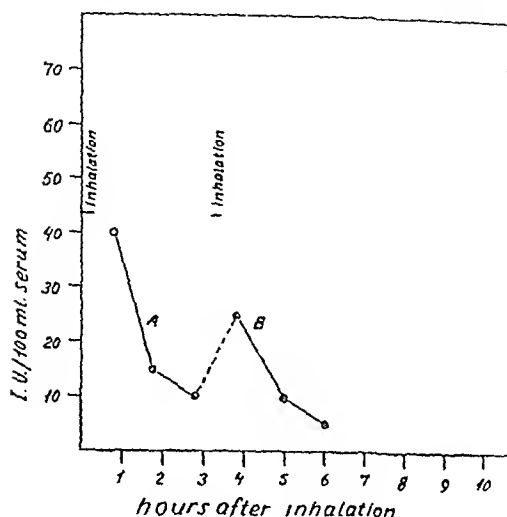


Fig. 9. Penicillin blood levels following the inhalation of 200,000 i. u. penicillin aerosol; A without and B with face mask.

tity of penicillin with and without glycerin — and without any difference observable in the penicillin-concentrations obtained.

The Importance of the Drop-Size, Experiments with Various Nebulizers.

Drops of widely different size are produced in every nebulizer. By means of a special construction of the nebulizer it is possible to a great extent to determine the size of the drops leaving it, but the nebula will, however, always consist of drops of very different radius. The size of the particle is quite decisive as to the places in the respiratory organs where the particles will stick and accordingly for the possibilities of local effect and resorption. This relation has been demonstrated experimentally, among others by Kaj Larsen & Niels Aage Nielsen (17) by investigations on resorption of adrenaline, and by van Wijk & Patterson (31) by investigations on the dust-particle-retention in the lungs. The same thing can also be proved by mathematical calculations and in this way Findeisen (9), has found the ensuing proportion between size of drop and precipitation at the different places in the respiratory system (table 1).

In order to obtain such a complete precipitation on an area as great as possible the nebulizer consequently has to produce particles of a radius of 1—3 micron. If it is wanted to have most

of it deposited at the bronchial wall the size of the particle should be bigger, about 10 micron.

Table 1.

Drop-size in relation to site of deposition in the air passages.

Drop-size (radius in micron)	Sito of dominating deposition
30 micron	Trachea
10 »	Bronchioli terminales
3 »	Ductuli alveolares
1 »	Sacculi alveolares, 2 % expired
0.3 »	Sacculi alveolares, 65.8 % expired
0.1 »	Sacculi alveolares, 65.0 % expired
0.03 »	Sacculi alveolares, 34 % expired

We have examined the drop-size of 4 various nebulizers (table 2).

Table 2.

The average drop-size in the mist delivered by the different nebulizers, measured by the glass slide method.

Nebulizer	Drop-size (radius in micron)
Hecto-spray	< 1—10 micron
Vaponephrin	2—10 »
DeVilbiss 40	3—15 »
DeVilbiss 16	50—300 »

The figures mentioned state radius of the particles in micron measured by ocular micrometer on glass slides after nebulization of concentrated malachite-green, the slides being held 1 cm in front of the mouth of the nebulizer. Radius has been corrected according to Huebner (13), on account of the flattening of the particles when they are beyond a certain minimal size. It is stated (2) that DeVilbiss 40 and the Vaponephrin-nebulizer produce drops with a radius of 0.7—1.9 micron; we cannot confirm these figures, but it must be emphasized that our method used for estimation of drop-size is very rough and gives an approximate survey only. The DeVilbiss 16 — giving rather a drizzle — is as a matter of fact not constructed for inhalation-treatment of the lower respiratory tracts, but has been used for this purpose in U. S. A. as well as in this country. DeVilbiss 40 is constructed as the Hecto-nebulizer. The Vaponephrin-nebulizer is built after

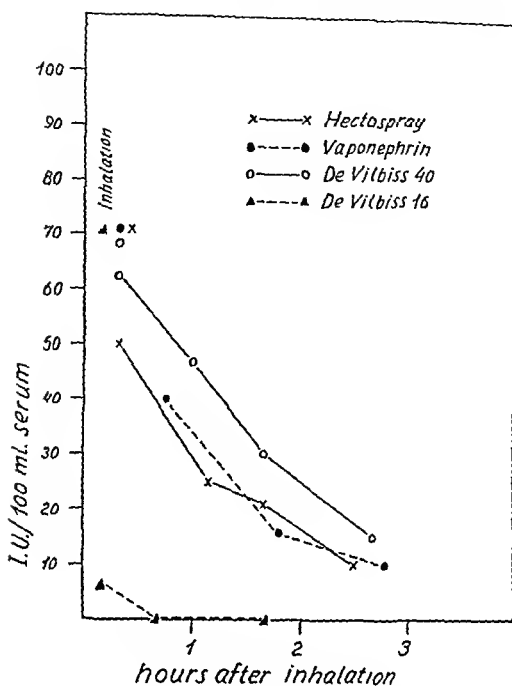


Fig. 10. Penicillin blood levels obtained by using various nebulizers, following the inhalation of 200,000 i. u. penicillin aerosol.

the same principle as are the others, the important point being a small glassball placed in front of the nebulizer.

We have examined the efficiency of the 4 nebulizers mentioned by following the blood-levels after inhalation of 200,000 i. u. of penicillin atomized by the various nebulizers (fig. 10).

The curves of the Hecto-nebulizer, the Vaponephrin-nebulizer, and the DeVilbiss 40 originate from the same volunteer and should accordingly be comparable. The DeVilbiss 40 is apparently somewhat superior to the Hecto-nebulizer and the Vaponephrin-nebulizer, the DeVilbiss 16 is quite out of the question, which fact also appears from fig. 11.

The various nebulizers empty themselves differently, the Vaponephrin-nebulizer is best, where one will find only a few % left after maximal emptying and ensuing rinsing and nebulization. The DeVilbiss 40 and especially the Hecto-nebulizer are rather slow in emptying themselves. To finish the inhalation within a reasonable time (30 minutes) you must make use of small quantities of concentrated solutions, by which the percental loss becomes greater.

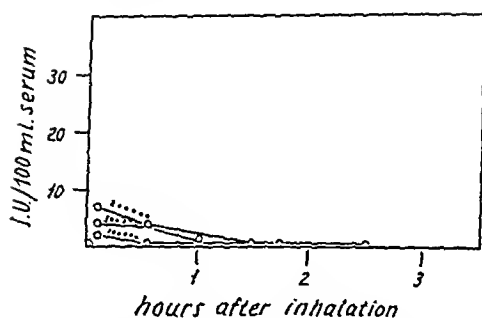


Fig. 11. Penicillin blood levels following the inhalation of 100,000—300,000 i. u. penicillin nebulized by DeVilbiss 16 atomizer.

Complications.

We have not observed any kind of unpleasantness by the inhalations — apart from a little trouble in the throat, especially after the DeVilbiss 16. Melanoglossia (7) has been reported after a prolonged treatment, possibly caused by a changed flora of the mouth (fungi). Allergic reactions in the form of urticaria and angioneurotic edema may be found after this as well as after other administration of penicillin (5, 27). Finally, as mentioned before, the possibility of local infection of the lungs must be stated, at worst sepsis caused by penicillin-resistant bacteria (coli) (14, 29), which may thrive greatly, if the penicillin-sensitive bacteria disappear during the treatment.

An essentially greater resorption than the one shown here can only be accomplished if it is possible to construct a nebulizer that will keep all the drops concerned in a definite size-order; the loss is especially determined by the too great drops caught inside or just below the glottis, where they can only produce a local effect.

Conclusion.

Except for the treatment of local infections in the respiratory tracts the inhalation-treatment will have no great possibilities to hold its own against the injection-treatment, which is cheaper and safer. Supposing that for some reason or other the injection cannot be carried through it is still possible to manage with inhalation alone.

Summary.

Through a series of experiments with inhalation of varying quantities of penicillin atomized by Vaponephrin-nebulizer it has

been found that about $1/6$ — $1/7$ only of the nebulized quantity can be traced in the blood.

It is possible — but expensive — to obtain high penicillin blood levels by inhalation.

Various experiments with modifications of the technique, including stabilization with 20 % glycerin, involve no changes of the quantity of penicillin resorbed.

Of various nebulizers the DeVilbiss 40 is found to give the best results.

In view of the present prices for penicillin the inhalation treatment will be of importance only in extraordinary cases, apart from local treatment of pulmonary diseases, where the method seems to be qualified.

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**Congenital Malformation of the Thorax
Accompanied by Congenital Vitium Cordis.
Attacks of Auricular Tachycardia.
Hemiplegia due to Crossed Embolism.**

By

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(Submitted for publication August 19, 1947.)

Within a short space of time we had the opportunity of observing a second case of the above combination. The case-history was as follows:

Boy, born 30. 6. 1933. Admitted 9. 1. 1947 to the R. C. Hospital in Sittard (ward for internal diseases).

Anamnesis (given by the mother): That morning the child had suddenly become paralysed; was unable to get out of bed. During the past few days he had suffered from a cold and lack of appetite. There was no cough. He had vomited that morning after breakfast. Had not suffered from headaches. The boy was incontinent of urine and faeces; he could not speak properly and his mouth was drawn to one side while the right arm and left leg were paralysed. There were pustules on the right leg. He had never been ill before, but was never really strong. He had not been in contact with any sick children. The father had died of peritonitis following an operation for ileus. The mother and 5 other children were healthy. There was no tuberculosis in the family. At school the boy, aged 14, had failed a few times to pass into a higher form and was now in the fifth. Had always been a solitary child.

Examination: A rather dull boy. Face slightly cyanotic in colour. Pulse: approx. 160'. Tension: not measurable left or right. Temperature on admission, rectal: 36.8°. Respiration: 34', superficial. Skin: ecchymatous ulcers on both legs. Height: 1.40 m. Weight: 31.4 kg. (N: 1.50 m.; 41 kg.) Mouth, teeth, tongue, tonsils were all normal.



Fig. I.

Skeleton (See photos Fig: I, II):

Thorax curved forwards and downwards; somewhat reminiscent of pyramidal thorax but with the difference that on our patient the top of the pyramid was divided into two and more cranially situated than in the classical pyramidal thorax. The sternal ends of the 3rd and 4th ribs projected distinctly beyond the surrounding area, forming the curvature of the anterior wall of the chest, described above, and being separated by a sternum with anterior convexity. The latter had no angulus Ludovici. The distance from the sternum at the level of the second rib to the point of the spinous process of the 5th dorsal vertebra was 15.5 cm. The distance from the highest point of the anterior wall of the thorax to the tenth dorsal vertebra was 20 cm. The maximum circumference of the thorax, measured over the two apices of the anterior wall was 67 cm at inspiration and 65 cm at expiration. The maximum transverse diameter, medioaxillary, was 21 cm. There was no spina bifida either in the dorsal or in the lumbo-sacral part of the spinal column. (X-ray photos by Dr. C. Bruin).

Lungs: percussion and auscultation; no abnormalities.

Heart: No voussure cardiaque. Apex-beat: 5th intercostal space, slightly to the outside of the medioclavicular line, frequent and heaving. Percussion: finger-breadth extension left and right. Dullness and flatness present. No sternal dullness above the origin of the great vessels. Auscultation: Very loud pulmonary second sound. Very rapid heart-action. No souffles.



Fig. II.

Abdomen; No abnormalities.

C. N. S. Pupil reflexes for light and convergence: normal.

Right side of the face hangs. Patient cannot put out tongue or swallow properly.

	Right	Left
Biceps reflex	—	+
Triceps reflex	—	+
Abdominal reflexes	≡	≡
Cremaster reflex	+	+
Knee tendon reflex	—	—
Achilles tendon reflex	—	—
Babinski reflex	+	—
Knee clonus	—	—
Foot clonus	—	—
Tonus, arms	<	n
Tonus, legs	<	n

Stiffness of neck: +? Kernig's sign: R: +; L: —.

Femoral pinching sign: R: —; L: +.

The sensibility of the right half of the body is apparently reduced. The boy can lift the right leg a little.

Fundus oculi: no abnormalities.

Cerebrospinal fluid (9.1.1947): Clear. Reactions of Nonne-Appelt and Pandy: —. Number of cells per mm³: 2. Sugar content: 0.693 %₁₀₀ (Hagedorn & Jensen). 10. 1. 1947: Sugar content: 0.750 %₁₀₀. No network after standing 24 hours. Urine: sp. gr. 1.020. Albumen: +. Reduction: —. Blood analysis (10.1.1947): Hgl: 122 % (corr., Sahli).

Erythrocytes/mm³: 7,220,000. Colour index: 0.84. Leukocytes: 10,900/mm³. Thrombocytes: 4,421,000/mm³. Basophile cells: 0 %. Eosinophile



Fig. III.

cells: 0 %. Staff cells: $12\frac{1}{2}$ %. Polynuclear cells: 67 %. Lymphocytes: 18 %. Monocytes: $2\frac{1}{2}$ %. Bleeding time: $1\frac{1}{2}'$. Coagulation time: $5\frac{1}{2}'$. Prothrombin time: 40". Rumpel-Leede: —. Sedimentation rate, erythrocytes: 0.5 and 1 mm after 1 and 2 hours respectively. Wassermann and Sachs Georgi reactions (blood): —, —. Reactions of Pirquet and Mantoux: —, —. Stomach contents, fasting: tuberculosis bacilli — (Ziehl antiformin preparations); Loewenstein culture: —.

X-ray photo of thorax Fig. III, IV (9. 1. and 15. 2. 1947): The thorax is long, narrow and barrel-shaped. The upper fields of the lungs, surrounded by the bony structure of the thorax, form a clear dome on both sides. There is a greatly enlarged heart shadow with strongly marked arch of the pulmonary artery. The bulb of the aorta is not visible. Two-thirds of the transverse section of the thorax is occupied by the maximum breadth of the heart. The right hilus is extensive but the shadow is not dense. Right and left lung are patchily marked, especially round the heart and origin of the great vessels. The diaphragm is rather low at the right side, but still somewhat higher than on the left.



Fig. IV.

Electrocardiogram: (14. 2. 1947): Fig. V. Heart reaction: regular, 88'; pronounced right preponderance. S-wave in lead I very large; R-wave very small. In lead III small R-wave; no S-wave. In the ascending branch of the S-wave in lead I and the descending of the R-wave in lead III is a notch. The P-wave is considerable in leads I and II, small in lead III, here and there biphasic. The T-wave is negative in leads I and II, weakly positive in lead III; in lead IV it is strongly positive.

P—R distance: 0.18". *QRS:* 0.06". *QRST:* 0.36".

Circulation times (20. 1. 1947): sodium fluorescein time: 20" (N: 25—30" or sometimes 15—20"); saccharine time: 12" (N: 5—14").

During observation attacks of auricular tachycardia, sometimes of short and sometimes of longer duration were noted. During such an attack the boy's face became somewhat bluer in colour than was already the case, with simultaneous appearance of pallor; he became dyspnoeic and lay back motionless on his pillow. The anterior wall of the thorax moved vigorously with the rapid heart action and pulsations were clearly visible in the jugular vein. Attempts to check the

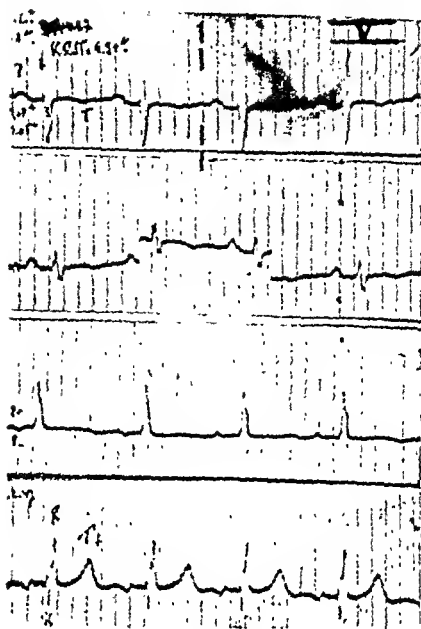


Fig. V.

attack by pressure on both eyeballs or the right sinus caroticus or by intravenous injection of 100 mg quinine sulphate were without effect.

An *E. C. G.* during such an attack showed the following:— (Fig. VI).

Frequency: 266'. High T-waves in leads I and II, negative in lead III, small in lead IV (T plus P?). In lead II the T-wave is notched. In lead II the descending branch of the R-wave has a distinct notch whilst the S-wave is absent. In lead IV the various complexes are of very variable aspect, presumably on account of the varying positions of the chest electrode relative to the heart at inspiration and expiration. The R-wave varies in size, in every fourth or fifth QRST-complex it is larger than in the preceding. In all complexes the R-wave is M-shaped. The Q-waves also vary in size, a high R being accompanied by a deep Q and a low R by a small Q. From the high R the ST segment runs above the isoelectric line; from the lower R it is isoelectric. In one place a P-wave is found in the T-wave of the preceding ventricular complex.

Diagnosis: Congenital deformity of the thorax combined with congenital vitium cordis. Open foramen ovale and interventricular septum. Attacks of paroxysmal auricular tachycardia; hemiplegia due to crossed embolism. Chronic pulmonary congestion. Polyglobulia rubra symptomatica.

The *prognosis* of this case is not too good. The *E. C. G.* for undisturbed action of the heart shows strong right predominance and — very important for prognosis — the T-waves are negative in leads I and II and very weakly positive in lead III.

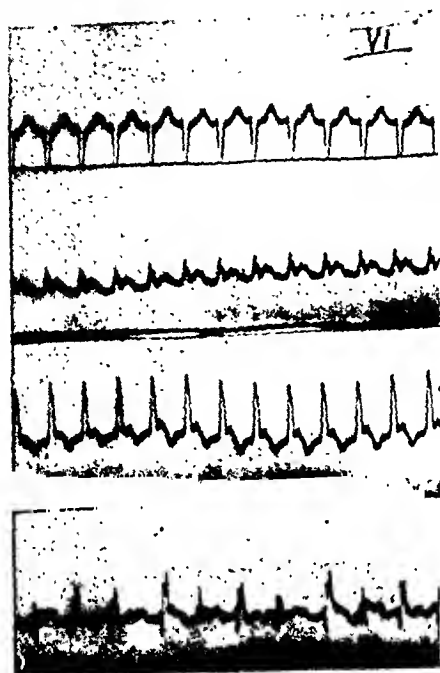


Fig. VI.

Treatment: (A) During the attacks we injected 0.5 cc coramine every three hours. An unsuccessful attempt was made to cut short an attack by intravenous injection of quinine sulphate (100 mg). We dared not use more than 100 mg in view of our previous unfortunate experience with a 19-year-old boy to whom we gave an intravenous injection of quinine solution on the attempt to check a protracted attack of paroxysmal tachycardia.

(B) Between attacks of tachycardia the patient's condition was reasonably satisfactory. He was mobilized by degrees and received 50 mg quinidine sulphate daily, leading to almost complete disappearance of the paroxysmal tachycardia. There could be no question of operative treatment for this boy. There was no open ductus arteriosus Botalli, no stenosis of the aortic isthmus and no Fallot's tetralogy. Moreover, the condition of the myocardium was not such as to permit of operation.

Discussion of Findings and Course of Disease.

According to the mother the thorax deformity had been present from birth. We examined the mother and the other five children, none of whom had the malformation of the chest found in our patient. On examination of the heart a pronounced pulmonary second sound was audible. The marked arching of the pulmonary artery, the right and left enlargement of the heart, the considerable polyglobulia of 7,200,000/mm³, the increased

haemoglobin content (122 per cent) and the marked right predominance in the E. C. G. formed a group of phenomena pointing to the existence of a congenital heart-defect, the exact nature of which could not be established with certainty. We were unable to sound the right side of the heart. The absence of souffles above the heart is quite compatible with a congenital defect, *e. g.* open foramen ovale, and does not conflict with this diagnosis.

The combination of a congenital true pyramidal thorax of familial occurrence with congenital vitium cordis was described by us some time ago (2). The case described here also furnishes clear illustration of the combined occurrence of congenital malformations of the heart and of the bony structure of the chest. At first, immediately after admission of this boy to hospital, we suspected an encephalitic process, cerebral haemorrhage or cerebral tumour as cause of the neurological signs. Encephalitis, however, could be excluded as the temperature and c. s. f. were normal. The bleeding, coagulation and prothrombine times and the number of thrombocytes were normal; the Rumpel-Leede sign was negative. There were, further, no signs to justify the assumption of haemorrhage in the capsula interna. The sudden onset rendered cerebral tumour improbable. At first we attributed the rapid action of the heart to an affection of the vagal nucleus; in view of the impaired powers of swallowing and speech we do not consider this unreasonable. The day after admission, however, when the pulse had suddenly dropped to normal frequency and the X-ray photos and E. C. G. diagrams had subsequently been studied, we were compelled to revise our provisional diagnosis and came to the conclusion that a *»paradoxical»* or *»crossed»* embolism from the right heart via a patent foramen ovale and/or interventricular septum offered a better explanation for the clinical picture observed. The fact that the circulation times were normal does not necessarily conflict with the existence of an open communication between the right and left sides of the heart, since if the left side of the heart is compensated the blood from the right side does not (or at any rate not to an appreciable extent) flow directly through to the left side but follows the normal route through the pulmonary circulation. Only rarely is the sodium fluorescein time found to be shortened where there is a short-circuit between the right and left halves. But even when the circulation time as a whole is normal, this *»normal»* figure may be the sum of a longer time in the peripheral, greater circulation, due

to decompensatio cordis, and a shorter time in the lesser circulation, due to a short-circuit in the form of patency of the foramen ovale and/or interventricular septum. Regarded in this light our values for circulation time are seen to be of little or no value for interpretation of clinical findings and diagnosis in cases of congenital defects of the heart.

The neurological signs gradually became stabilized. On the occasion of the most recent examinations (20. 3. 37. and 20. 4. 47) the following abnormalities of the right side of the body, were observed (our diagnosis was confirmed by the neurologist, J. G. Y. de Jong, Heerlen):

Moderate facialis paresis. Optokinetic nystagmus. The tongue is diverted slightly to the right when extruded. The right arm is held in a position of flexion and pronation. Arm and leg reflexes are strongly positive on the right. The reflexogenic zone of the right leg extends over the entire tibia. Distinct knee and foot clonus are present on the right. The reflexes of Babinski, Rossolino, Bechterew, Chaddock, Oppenheim and Gordon are positive on the right and there is a slight fan sign. As regards mental condition, boy is uncontrolled emotionally and in expression. He tends to make jokes and have uncontrollable fits of laughter. He repeats his words and short, affable phrases. For these reasons we are compelled to include an affection of the cerebral cortex in our diagnosis. The other boys in the ward make fun of him and find him »queer»; children are often mercilessly sharp in their judgements.

Summary.

A case is described of congenital deformity of the thorax combined with congenital vitium cordis.

The patient, a 14-year-old boy, suddenly developed hemiplegia due to crossed embolism, in all probability during an attack of paroxysmal auricular tachycardia.

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Uebergang einer essentiellen hypochromen Anämie in perniciöse Anämie mit Vermehrung der gewebibasophilen Zellen im Sternalpunktat.

Zugleich ein Beitrag zur achrestischen Anämie.

Von

Privatdozent Dr. ST. J. LEITNER.

(Bei der Redaktion am 1. August 1947 eingegangen.)

I.

Übergang einer essentiellen hypochromen Eisenmangelanämie in Perniziosa wurde in der Literatur wiederholt beschrieben (Miller und Dameshek, Waldenström, Witts, Schulten, v. Jagic und Klima, Meulengracht, Lenhartz, Heilmeyer). Immerhin ist dieses Ereignis nicht sehr häufig. Wenn wir die Ursachen beider Krankheiten in einer einfachen Minderleistung des Magen-Darmkanals erblicken, so sollten solche Übergänge häufiger zur Beobachtung gelangen. Die grosse Bedeutung der Defizienz der Magenfunktion ist bei der essentiellen Eisenmangelanämie seit der Arbeit von Kaznelson, Reimann und Weiner (1929), in welcher der Salzsäuremangel im Magensekret in den Mittelpunkt gestellt wurde («achylische Chlorämie»), gut bekannt. Der von Kaznelson und Mitarbeitern gegebene Name konnte sich nicht durchsetzen, weil Schulten, Bode und Heyrodt u. a. gezeigt haben, dass die Anazidität keine obligate Voraussetzung der Anämie ist, die Dameshek als «idiopathischen», Schulten als «essentielle» *hypochrome Anämie* bezeichnet haben. Sicher ist die Anazidität aber häufig, sie ist nach Lundholm in 67 %, nach Hartfall und Witts sogar in 80 % der Fälle nachweisbar. Dieser Mangel an Salzsäure ist

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die Ursache der ungenügenden Ionisation des Nahrungsseisens im Magen (Morley, Hemmeler), so dass es infolge der schlechten Resorption zu einer Eisenmangelanämie kommt (Bethel, Goldhamer, Isaacs und Sturgis, Heilmeyer, Vannotti und Delachaux, Leitner u. a.). Im Experiment zeigen Achylische bei einer täglichen oralen Zufuhr von 11 mg Eisen eine negative Bilanz von 4 mg, während Normazide bei einer täglichen Zufuhr von 10 mg eine um 1 mg positive Bilanz aufweisen. (Fowler und Barer.) Einen weiteren Beweis für die Bedeutung der Magensäure bildet der Nachweis der guten Eisenresorption bei Kranken nach Magenresektion durch *intravenöse* Belastungsversuche (Hemmeler). Die Anämie ist danach nicht eine Folge der schlechten Eisenverwertung, sondern der ungenügenden Resorption infolge der Magenresektion. Auch klinische Beobachtungen weisen in diese Richtung, da nach Magenresektion und Abnahme der Salzsäuresekretion im Magen in einem Drittel (Riedel, Gordon-Taylor, Morley und Roberts) oder sogar in der Hälfte der Fälle (Gutzeit, Dedichen) eine, meist hypochrome, Anämie beobachtet wurde. Dass sich in einem Teil der Fälle trotz der Anazidität keine Anämie entwickelt, zeigt nur, dass der Mangel an Magensäure keine ausschliessliche, sondern nur eine wichtige Ursache der Blutarmut ist. Dafür sprechen auch die Beobachtungen, dass bei der e. h. A. Eisen auch ohne Salzsäuregaben wirkt, wenn auch in höheren Dosen unvollkommener (Heilmeyer und Plötner, Moore und Mitarbeiter, Skouge, Leitner u. a.).

Bei der *perniziösen Anämie* ist die Bedeutung der intakten Magensekretion noch unumstrittener, gehört doch die Achylie schon seit jeher zu den Kardinalsymptomen des Morbus Biermer-Addison. C. Gessler¹ hat jüngst die Literatur über die Entstehung der Perniziosa nach Magenresektion kritisch gesichtet, sie findet sich zum Teil auch in unserer Knochenmarksmonographie. Es

¹ 1. Gessler, C. J.: Vlaamsch Geneesk. Tijdschr. 1939, Nr. 47. — 2. Hartmann, H. R.: Amer. J. med. Sc. 162, 201 (1921). — 3. Dennig, H.: Münch. med. Wschr. 1929, 633. — 4. Breitenbach, G.: Münch. med. Wschr. 1929, 1920. — 5. Poole, A. K. und Foster, L. C.: J. amer. med. Assoc. 96, 2187 (1931). — 6. Ungley, C. C.: Newcastle med. J. 12, 192 (1932). — 7. Lobenhoffer, W.: Münch. med. Wschr. 1934, 157. — 8. Delore, P.: Lyon Méd. 141, 601 (1928). — 9. Hochrein, M.: Münch. med. Wschr. 1929, 1327. — 10. Morawitz, P.: Arch. Verdauungskrh. 47, 305 (1930). — 11. Scheidel, H.: Med. Klin. 1930, 247. — 12. Berger, L.: Med. Klin. 1931, 171. — 13. Conner und Birkeland: Ann. int., Med. 789 (1933). — 14. Wilkinson, J. F.: Quart. med. J. N. S. 2, 281 (1933). — 15. Goldhamer, S. M.: Surg., Gyn. u. Obstetr. 57, 257 (1933). — 16. Wotzka, K.: Dtsch. med. Wschr. 1935, 1548. — 17. Teufl, R.: Arch. Verdauungskrh. 61, 166 (1937). — 18. Lacroix, W. und Koek, H. C.: Nederl. Tijdschr. Geneesk. 81, 2221 (1937). — 19. Buchgraber, K. und Fleischhacker, H.: Wien. Arch. inn. Med. 32, 33 (1938).

wurde sowohl nach partieller (2—7), als auch besonders nach totaler (8—19) Magenresektion eine Perniziosa beobachtet. Die Verhältnisse liegen aber nicht so einfach, dass man sagen könnte, dass bei alleinigem Fehlen der Magensäure (Anazidität) eine Eisenmangelanämie, bei kompletter, histaminrefraktärer Achylie eine Perniziosa entsteht. Seit den Untersuchungen von Castle und Mitarbeitern wissen wir, dass der Mangel am intrinsic Factor im Magensaft Ursache der p. A. ist. Die Achylie geht aber nicht immer mit einem Versiegen des intrinsic Factors einher, konnte doch bei der essentiellen Eisenmangelanämie in 40 % der Fälle eine komplette Achylie nachgewiesen werden. Ob sich allerdings in diesen Fällen mit der Zeit eine p. A. entwickelt, ist noch unbekannt. Wenn mit der Achylie nicht zwangsläufig ein Mangel am intrinsic Faktor einhergeht, so fanden wir auf der andern Seite bei jeder gastrogenen Perniziosa eine Achylie. Mit anderen Worten: Eine Achylie mit noch genügender Produktion des intrinsic Faktors ist möglich, sogar relativ häufig, ein Versiegen des Castle-Faktors ist dagegen immer mit Achylie verbunden, sodass, falls eine Reihenfolge überhaupt aufgestellt werden kann, sich die Insuffizienz der Magensekretion graduell wie folgt entwickelt: Anazidität → Achylie → Mangel am intrinsic Faktor. Dabei lassen wir den Magenschleim, der nach Minot, Heath, Mahlo, Pohle, Altstedt bei der Entstehung der e. h. A. eine Rolle spielt, ausser Betracht, ebenso die Auffassung von Wollheim, der ausser dem Castle-Ferment und dem Addisin im Magensaft einen dritten für die Erythropoiese wichtigen Faktor annimmt, auch wenn diese in der angeführten Reihenfolge Zwischenstufen bilden können.

Dass diese Reihenfolge den tatsächlichen Verhältnissen wahrscheinlich am besten entspricht, zeigt der Umstand, dass ein Übergang der essentiellen Eisenmangelanämie in Perniziosa, mehrfach, der umgekehrte Vorgang, der spontane Übergang der Biermer'schen Anämie in eine essentielle hypochrome Anämie dagegen nie beobachtet wurde; die Reihenfolge ist also nicht reversibel. Der Eisenmangel am Ende der Leberbehandlung der Perniziosa, der eine Folge der überstürzten Regeneration und der dadurch bedingten Erschöpfung der Eisenreserven ist (vergl. Leitner »Die intravitale Knochenmarksuntersuchung«), lassen wir hier ausser Betracht, weil es in diesem Zusammenhang nur auf die spontane Entwicklung ankommt.

In dieser Mitteilung möchten wir über einen jahrelang beobachteten Fall von Übergang einer essentiellen, hypochromen

Anämie in Perniziosa berichten, bei dem wir im Sternalpunktat einen neuen, bis jetzt nirgends beschriebenen Befund mit reichlichen *Gewebsbasophilen* erheben konnten. Die Überlassung der Krankengeschichten verdanke ich Herrn P. D. Dr. Bannmann, Chefarzt des Bezirksspitals Langenthal.

II. Krankengeschichte.

Es handelt sich um eine 1895 geborene Hansfran (G. E.), in deren Familie ein Todesfall an Blutkrankheit vorgekommen ist. Näheres über die Natur der Blutkrankheit konnte nicht ermittelt werden. Pat. selbst soll von Jugend auf blutarm gewesen sein, ihr Hämoglobin ging nach den behandelnden Ärzten nie über 55/70 hinaus. Pat. hat geheiratet und hatte 3 normale Geburten, die letzte 1929, bei der sie einen grossen Blutverlust und Puerperalfieber mit Herzklappenentzündung hatte, weshalb sie mehrere Monate im Spital lag.

Infolge der Anämie fühlte sich Pat. seit jeher müde, nicht leistungsfähig, litt an Schwindel, bei Treppensteigen an Atemnot, an Neigung zu Durchfällen und seit der letzten Geburt auch an Knöchelödemen.

1940 Spitalaufenthalt wegen Strumektomie. Grundumsatz vor der Operation zwischen + 24 und + 32, nach der Strumektomie + 12. Die histologische Untersuchung der exstirpierten Schilddrüsenpartien ergab eine Struma colloidosa basodiflicata (Path. Institut, Univ. Bern, Prof. Dr. Wegelin). Anämie mit 3.4 M. Erythrocyten und 55.70 Hb (s. Tabelle 1).

30. 9.—1. 10. 42 stationäre Krankenhausbehandlung wegen allgemeinen Beschwerden wie Müdigkeit, Schwindel, Schluckbeschwerden. Die klinische Untersuchung ergibt Folgendes: Grosse, sehr blassc Frau in reduziertem Ernährungszustand. Eigentümliche, bräunliche Pigmentierung des Gesichtes, Conjunctivae anämisch, Skleren weiss, reaktionslose Strumektomienarbe. Herz mitral konfiguriert, vergrössert lautes systolisches Crescendogeräusch über der Spitze, Pulmonakton gegenüber dem II. Aortenton accentuiert, Blutdruck 160/100 mm Hg. Venektasien am Unterschenkel, Abdomen o. B. Anämie mit 3.3 M. Erythrocyten und 45/70 Hb., Farbindex 0.91. Keine Besserung der Anämie auf Eisen- und Leberpräparate. Konsultation einer Med. Univ.Klinik, wo die Diagnose einer essentiellen Eisenmangelanämie gestellt wird.

23. 8. 46—3. 10. 46 erneut stationäre Behandlung wegen Apoplexie. In letzter Zeit zunehmende Verschlechterung des Allgemeinzustandes, oft Kopfschmerzen und Schwindel. Ab und zu Erbrechen, Blutdruck zeitweise sehr hoch. Objektiv war der Ernährungszustand relativ ordentlich, Hände und Skleren wiesen eine leicht gelbliche Farbe auf, Schleimhäute blass. Herzbefund mit der Mitralconfiguration und mit dem systolischen Geräusch unverändert, Blutdruck 145/70 mm Hg. Leber 2 Querfinger unterhalb des Rippenbogens, Milz perkussorisch etwas vergrössert, aber nicht palpabel. Urin: Urobilin und Urobilinogen positiv, sonst o. B. Magenchemismus: Histaminrefraktäre Achylie mit

Tabelle 1.

Tabelle 1.

Zellart	D a t u m										
	1940		1942				1946				
	1. X.	2. XI.	28. VIII.	30. IX.	29. X.	9. XII.	24. VIII.	6. IX.	13. IX.	20. IX.	30. X.
Erythrozyten	3.4 M	3.312	3.5	3.9	4.6	3.5	1.9	1.61	1.78	2.35	2.4
Haemoglobin	55/70	50/70	45/70	42/70	60/70	55/70	42 %	45 %	48 %	49 %	52 %
Färbeindex...	10.4	0.93	0.9	0.77	0.92	1.11	1.1	1.4	1.3	1.03	1.1
Retikulozyten							+++	+++	+++	++	+
Anisozytose	(+)	(+)	+	(+)	(+)	(+)	++	++	++	+	+
Poikilozytose	—	—	(+)	—	—	—	—	—	—	—	—
Mikrozytose	+	+	+	++	+	+	++	++	++	+	+
Megalozyten	—	—	—	—	—	—	4,650	4,200	4,950	6,100	4,100
Leukozyten...	5,500	4,800	6,000	5,700	5,400	5,200					
davon:											
Basophile ...	0.5	0.5	0.5	—	1.0	—	—	0.5	—	0.5	—
Eosinophile...	6.5	4.5	7.0	—	5.5	2.5	2.0	6.5	6.5	8.0	8.0
Stabkernige	—	—	—	—	2.0	—	—	2.5	1.5	1.5	1.0
Segmentkernige ...	50.5	52.5	50.0	63.0	49.5	64.0	55.0	51.0	54.0	53.5	46.0
Lymphozyten	34.0	37.0	33.0	28.0	37.0	25.0	42.0	36.5	32.0	30.0	38.5
Monozyten ..	8.5	5.5	9.5	7.5	4.5	8.5	1.0	3.0	6.0	6.0	6.5
Plasmazellen	—	—	—	—	0.5	—	—	—	—	—	0.5
Thrombozyten	norm.	norm.	norm.	norm.	reichl.	norm.	vermindert		vermindert		60,00
Übersegmentierung ...	(+)	(+)	(+)	(+)	—	(+)	++		++		+
Therapie	Ferroeisen		Ferro-Eisen, Heparglandol forte.				Heparglandol forte,		Heparglandol forte, Pernaemon forte, Ventrepar, Becocym (Vit. man B kompl.)		+

... für das HCl-Defizit

einem Höchstwert für Gesamtazidität von 15 und für das HCl-Defizit von — 25.

Neurologisch: Parästhesien am linken Bein und Arm, Periostreflexe an den Vorderarmen gesteigert, Bauchdeckenreflexe nicht sicher auslösbar, Patellarreflexe gesteigert, Spontanbabinski. Im Stuhl Ascarideneier, auf Chenosankur Abgang von 6 Ascariden. Starke Anämie mit 1.9 M. Erythrocyten und 42 % Hämoglobin. Auf Heparglandol schwere allergische Reaktion, deshalb Wechsel des Präparates. Ventrepar und Pernaemon werden gut vertragen und führen zu leichter Besserung. Die Blutbefunde zeigt folgende Tabelle 1.

Wie wir aus der Tabelle 1 ersehen, lag 1940 und 1942 eine mässige hypochrome Anämie mit Anisocytose und Mikrocytose vor, die auf Eisen- und Leberpräparate kaum ansprach. Im weissen Blutbild bewegten sich die Leukocytenzahlen eher an der unteren Grenze der Norm, 1940 mit einer leichten Lymphocytose, die bei 2 Auszählungen auch 1942 erkennbar ist. Hie und da fand sich auch eine leichte Eosinophilie, die schon vor der Lebertherapie festgestellt wurde. Unter den Leukocyten zeigten sich

immer Übersegmentierte und Thrombocyten waren reichlich vorhanden. Obschon damals keine Serumeisenbestimmung vorgenommen wurde, sprechen die Befunde für eine essentielle hyperchröme Anämie. Mit dieser Diagnose stehen auch die klinischen Befunde in Einklang, Adynamie, Blässe ohne gelbliche Färbung, Schwindel, Andeutung des Plummer-Vinson Syndroms, Beschleunigung der Darmpassage, fehlende Urobilin- und Urobilinogenurie.

Bei den Untersuchungen 1946 konnte nun eine einwandfreie perniziöse Anämie festgestellt werden. Klinisch waren neben den Allgemeinerscheinungen (Müdigkeit, Appetitlosigkeit usw.) die strohgelbe Haut- und Sklerenverfärbung, Urobilin- und Urobilinogenurie, histaminrefraktäre Achylie, hämatologisch eine hyperchrome Anämie mit typischen Megalocyten, Leukopenie mit relativer Lymphocytose und Thrombopenie feststellbar. Die Therapie bestand von Anfang an in Eisen- und Leberpräparaten in genügender Dosierung, ferner in Vitaminpräparaten, namentlich des B-Komplexes. Der therapeutische Erfolg war aber jeweils nur sehr geringfügig, eine Kompensierung der Anämie konnte nicht erreicht werden. Die morphologischen Erscheinungen, die Parästhesien am linken Bein und Arm, sowie die Reflexsteigerungen, die wahrscheinlich nicht auf die angenommene Apoplexie, sondern auf eine funikuläre Myelose zurückzuführen sind, haben sich gebessert. Immerhin ist hier auch die spontane Besserung der Folgen einer leichten Apoplexie nicht auszuschliessen. Leider stand damals Folsäure noch nicht zur Verfügung, durch die bei manchen »therapierefraktären« (Rhoads) Anämien noch ein Erfolg zu erzielen ist. Da kein deutlicher Milztumor vorlag und eine Hämolyse nicht im Vordergrund stand, kam eine Splenektomie nicht in Betracht. Endgültig wurde die Diagnose durch Sternalpunktion gesichert, die eine Erythroblastenvermehrung mit zahlreichen typischen Megaloblasten, ferner eine Linksverschiebung der Granuloblasten sowie sehr spärliche Megakaryocyten ergab.

Sternalpunktat: Proerythroblasten 22, Makroblasten 28, Normoblasten 60, Megaloblasten 64, Myeloblasten 1, Promyelocyten $4\frac{2}{3}$, neutro. halbreife Myeloc. $7\frac{1}{3}$, reife Myeloc. 15.0, Metamyeloc. $22\frac{1}{3}$, Stabkernige $13\frac{2}{3}$, Segmentkernige 11, eos. Myeloc. $1\frac{1}{3}$, Metamyeloc. $3\frac{1}{3}$, Reife $4\frac{2}{3}$, Lymphocyten 2.0, Monoc. 1.0, Megakaryoc. $\frac{1}{3}$, Proplasmocyten $\frac{2}{3}$, Plasmocyten 1.0, junge Retikulumzellen 2, phagocytierende Ret.z. 2.0, Gewebsbasophile $5\frac{2}{3}$ %, Mitosen der Roten $3\frac{2}{3}$, der Weissen $1\frac{1}{3}$ %. Grosse Neutrophile, grosse Retikulumzellen.

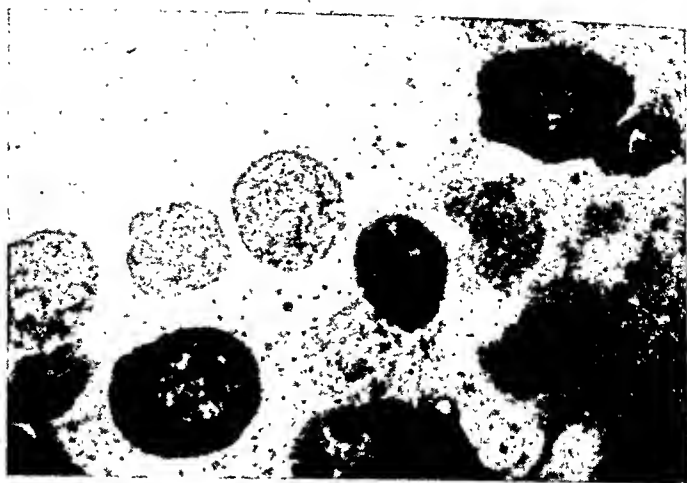


Abb. 1. Drei Gewebsbasophile im Sternalpunktat in einem Gesichtsfeld (s. Text).

III. Morphologie und Bedeutung der Gewebsbasophilen.

Was den Sternalmarkbefund besonders interessant macht, ist das reichliche Vorhandensein der *Gewebsmastzellen*, das beim Morbus Biemer offenbar bis jetzt noch von keiner Seite beobachtet wurde. Das Mikrophotogramm zeigt ein Gesichtsfeld mit 3 solchen Zellen (Abb. 1). Die Diagnose der Gewebsbasophilen stösst auf keine Schwierigkeiten. Als ihre Merkmale haben wir in unserer Knochenmarksmonographie hervorgehoben, dass ihr Kern meist relativ klein und chromatinreich, ihr Protoplasma durch die dichte, schwärzliche weich-konfluierende Granulation gekennzeichnet ist, während die Blutbasophilen einen relativ chromatinarmen Kern haben, der bei deren Vorstufen relativ gross ist und den grössten Teil der Zelle einnimmt. Die Granula der Blutbasophilen sind verschieden gross, hart-violett, konfluieren nie, oft sind sie spärlich, weil der Methylalkohol sie bei der Fixation auswäscht. Undritz¹ wies auf die letztere Eigenschaft nachdrücklich hin und spricht von löslicher und unlöslicher Granulation der beiden basophilen Zellarten, umsomehr als letztere Zellen nur beim Menschen im Blut fehlen, während sie bei gewissen Tieren (Mäusen, Ratten, wirbellose Tiere) ins Blut gelangen können. Wenn wir die Unterschiede schematisch darstellen wollen, so ergibt sich folgendes:

¹ Undritz, E.: Schweiz. med. Wschr. 1946, 88, 115.

Tabelle 2.

	Blutbasophile	Gewebsbasophile
Vorkommen	im Blut und im Knochenmark, bei gewissen Leukämieformen zahlreich, besonders nach Bestrahlung.	In der Milz, Leber, seltener im Knochenmark
Kerneigenschaften	Kern bei der Giemsa- oder bei der panoptischen Färbung mit May-Grünwald-Giemsa-Lösung eher chromatinarm, hell. Die reifen Formen zeigen Kernpolymorphie, die Kerne der jungen Formen sind gross. Struktur feinretikulär.	Rund, im Verhältnis zum Protoplasma relativ klein, chromatinreicher als die Blutbasophilen, Struktur eher kompakt, grobschollig.
Protoplasma	Granula violett, rund, ungleich gross, hart, von einander gut abgrenzbar, manchmal spärlich.	Granula fast schwarz, weich, dicht konfluierend, nimmt das ganze Protoplasma ein.
Löslichkeit	Granula durch Methylalkohol teilweise ganz aufgelöst, so dass die Granula, besonders bei einfacher Giemsa-Färbung grösstenteils fehlen. Bei der Färbung mit May-Grünwald-Lösung nach Pappenheim bleiben sie erhalten. Die Löslichkeit ist bei den reifen Leukoeyten stärker als bei den Myeloeyten.	Granula nicht löslich, bleiben bei Methylenalkoholbehandlung unverändert.
Funktion	Wahrscheinlich Heparinbildung.	Wahrscheinlich Heparinbildung (1-7). ¹ Toluidinblaureaktion positiv.
Oxydase- oder Peroxydase-reaktion	In der Regel negativ.	Immer negativ.

Die Morphologie und teils auch die Funktion der von Ehrlich entdeckten Mastzellenarten sind geklärt, ihre pathognomonische Bedeutung im Knochenmark ist aber noch unbekannt. Die Gewebsbasophilen wurden im Mark zuerst von Rohr als basophile Kugeln, dann von Moeschlin, Undritz sowie Leitner beschrieben und abgebildet.

Besonders interessiert uns hier die Frage, ob die Gewebsbasophilen im Sternalpunktat im vorliegenden Falle einen Zufallsbefund darstellen, oder ob ihnen eine pathognomonische Bedeu-

¹ 1. Holmgren, H. und Wilander, O.: Z. mikr.-anat. Forsch. 42, 242 (1937). — 2. Howell, W. H. und Holt, E.: Amer. J. Physiol. 47, 328 (1918). — 3. Lison, L.: I. Bull. d. l. classe des sci. Brux. 19, 1332 (1933) und 20, 1160 (1934). — 4. Jorpes, E.: Biochem. Z. 28, 1817 (1935); Naturwiss. 23, 196 (1935). — 5. Bergström, S.: Naturwiss. 23, 706 (1935); Z. physiol. Chem. 238, 163 (1936). — 6. Sylvén, B.: Acta Chir. Scand. (Suppl.) 86, Suppl. 66 (1941). — 7. Schürer, W.: Helv. med. Acta 13, 161 (1946).

tung zukommt. In unserer erwähnten Monographie haben wir einen Fall von chronischer Panmyelopathie bei Lungentuberkulose beschrieben, bei der die Anämie und auch die Granulocyto- und Thrombopenie sehr therapiéresistent waren und sich zunächst auch nach erfolgreicher Behandlung der Tuberkulose mit extra-pleuralem Pneumothorax nicht besserten. Seither erhielten wir die Nachricht, dass es der Patientin gut gehe. Undritz¹ misst den Gewebsbasophilen besonders bei der Panmyelopathie bei Reduktion des neutrophilen Systems (Agranulocytose, lymphatische Leukämie) eine diagnostische Bedeutung bei. In unserem vorliegenden Falle steht die hyperchrome Anämie im Vordergrund, die Schädigung des Granulocytensystems ist sehr geringfügig. In Analogie zu unserem früher beschriebenen Fall chronischer Panmyelopathie möchten wir die Gewebsbasophilen als Zeichen der besonderen Torpidität der Anämie und ihrer geringen therapeutischen Beeinflussbarkeit ansehen. Ob diese Torpidität auf einen Infekt zurückzuführen ist, wie im früheren Fall, ist schwer zu sagen, weil ein offensichtlicher Infekt nicht aufzudecken war; ein Foka infekt ist freilich trotzdem nicht auszuschliessen. Die frühere Hyperthyreose spielt dagegen wahrscheinlich keine Rolle, da seit der vor 6 Jahren vorgenommenen Strumektomie keine Zeichen eines Morbus Basedow bestehen und der Grundumsatz war auch normal (+ 12).

Einem Infekt kann eine Bedeutung für die Entstehung der Perniziosa hier nur in dem Masse zugestanden werden, dass er zu einer chronischen Gastritis und schliesslich zu einer Achylie führt, die beim Fehlen des Castle-Faktors Ursache der Perniziosa ist. Eine solche Deutung erscheint im vorliegenden Falle nicht unberechtigt, da die 1940/42 festgestellte hypochrome Anämie dafür spricht, dass damals keine komplette Achylie (jedenfalls nicht mit Fehlen des Castle-Fermentes) bestand, sondern eine allmähliche aber progressive Schädigung der Magensekretion bis zur histaminrefraktären Achylie naheliegend ist. Die Frage, ob eine Infektionskrankheit durch toxische Markschädigung zu einer hyperchromen Anämie vom Typus der Perniziosa führen kann, sei jetzt nicht näher erörtert. Als Kriterium muss für solche Fälle das Fehlen der Achylie und das Vorhandensein des Castle-Fermentes im Magensaft gefordert werden. Bei Erfüllung dieser Forderung bleiben sicher nur *wenige infektbedingte Perniziosafälle* übrig, die einer Kritik standhalten und bei denen eine *mangelhafte*

¹ Undritz, E.: l. c.

Utilisation des Antiperniziosaprinzijs im Knochenmark angenommen werden muss. Der Herzfehler und die Hyperthyreose spielen aetiologisch sicher keine Rolle.

Auf andere Ursachen der essentiellen Eisenmangelanämie und der Perniziosa sind wir hier absichtlich nicht eingegangen, diesbezüglich sei auf unsere Monographie verwiesen. Es sei lediglich erwähnt, dass konstitutionelle Faktoren bei beiden Krankheiten eine Rolle spielen und dass in gewissen Fällen die Schädigung viel tiefergreifend ist, als es auf den ersten Blick erscheint. In unserem Falle spricht die seit der Kindheit bestehende Anämie für die mögliche Bedeutung der Konstitution und vor allem für die langsame Entwicklung der Krankheit in die Richtung der Perniziosa mit wahrscheinlicher progressiver Schädigung der Magensaftsekretion. Es wäre vielleicht von Interesse, wenn bei der Perniziosa Fälle bekannt gegeben werden könnten, die viele Jahre hindurch vor dem Auftreten der hyperchromen Anämie verfolgt worden sind; vielleicht könnte dann vielfach ein »praeperniziöses (hypochromes) Stadium« der Anämie und der Magensekretionschädigung entdeckt werden. Bei dieser Überlegung wäre auch verständlich, dass die Perniziosa eine Alterskrankheit ist und bei Jugendlichen nur ausnahmsweise beobachtet wurde. Hierbei denken wir immer an die kryptogenetische (gastrogene) Perniziosa, da eine hyperchrome megalocytaire Anämie, die auch zur Gruppe der p. A. gehört, aus Mangel an dem extrinsie Faktor (»tropische megalocytaire Anämie« von Wills und Mitarbeitern) oder infolge toxischer Einflüsse (Bothriocephalusanämie) oder infolge Mehrverbrauch (Gravidität) auch bei Jugendlichen entstehen kann. Es ist klar, dass es Fälle gibt, bei denen die Mageninsuffizienz nie über den Säuremangel hinaus geht, sodass die hypochrome Eisenmangelanämie bis zuletzt besteht. Dass bei der Perniziosa, wenn sie einmal in Erscheinung tritt, der Eisenmangel trotz der schlechten Eisenbewertung nicht mehr besteht ist verständlich, weil der Serumeisenspiegel infolge der Hämolyse hoch ist.

Der Fall bildet ferner einen Beitrag zum Verständnis der *achrestischen Anämie*, bei der es sich nach Israels und Wilkinson (Quart. med. J. N.s 5, 69, 1936) um eine megaloblastische hyperchrome Blutarmut handelt, die auf Leberpräparate nicht anspricht, weil das Leberprinzip im Knochenmark nicht verwertet wird. In den Fällen von Israels und Wilkinson sowie Zanaty (Lancet 1937 II, 1365) war im Magensaft freie Salzsäure vorhanden, wie auch in den Beobachtungen von infektbedingten hyperchromen

Anämien vom Perniziosatyp, die vereinzelt beschrieben wurden. Indessen wurde auch achrestische Anämie mit Achylie beobachtet (A. A. Huse: Brit. med. J. 1944 I, 184) und unseres Erachtens sollte bei der Zuordnung zur achrestischen Anämie nicht die Achylie, sondern die mangelhafte Utilisation des Antiperniziosastoffes in Knochenmark die Hauptrolle spielen. In unserem vorliegenden Falle haben wir sowohl die Achylie, als auch die mangelhafte Verwertung des Leberprinzipes im Mark auf die gleiche chronische Schädigung (Fokalinfekt) zurückgeführt. Von besonderer Bedeutung ist es aber, dass in unserem Falle zum ersten Male ein Sternalpunktatbefund erhoben werden konnte, der für eine tiefgreifende Markschädigung spricht und das refraktäre Verhalten des Knochenmarkes auf Leberpräparate erklärt: Die Vermehrung der gewebssasophilen Zellen. Die achrestische Anämie wird vielfach mit der aplastischen oder aregeneratorischen Anämie identifiziert, was aber unseres Erachtens nicht berechtigt ist, weil man zur achrestischen Anämie nur die Fälle mit dem typischen hämatologischen Befund der perniziösen Anämie (Hyperchromie, Megalozyten im Blut, Megaloblasten im Mark) zurechnen kann. Bomford und Rhoads betrachten die achrestische Anämie als eine Form ihrer »refractory Anämie«, während wir nach der vorliegenden Beobachtung glauben, dass der Begriff der achrestischen Anämie berechtigt ist, auch wenn ihr Kreis durch Nachweis von komplizierenden Infektionskrankheiten (bei p. A.) oder durch Entdeckung neuer therapeutischer Mittel (Folic acid) eventuell eingeengt wird.

Summary.

A case of idiopathic hypochromic anemia developed all the typical features of pernicious anemia with a high colour index, megalocytes and megaloblasts. Sternal puncture showed the characteristic megaloblastic marrow and a shift to the left of the granuloblastic series with giant forms and an increase of the tissue mast cells (see photomicrograph!). This feature has so far not been described in cases of pernicious anemia. It may explain the only slight response obtained from liver, iron and Vitamin B therapy. In our experience increases of tissue mast cells only occur in severe marrow upsets, such as panmyelopathy. It is uncertain, whether the resistance to treatment was caused by a chronic (? focal) infection, which might have led to

hypofunction of the gastric juices. We believe, that this disorder of the gastric function occupies the key position in the problem presented by this case. It is probable, that exhaustion of the production of acid in the stomach was the first pathological change, leading to insufficient ionisation and further to poor use being made of the iron supplied in the food. This may explain the development of hydrochromic anemia. Later on the intrinsic factor may have become lacking and the case was transformed into one of pernicious anemia.

If we accept the theory of the gastric basis in the aetiology of certain forms of hypochromic iron-deficiency anemias, and of pernicious anemias, it is possible, that a hypochromic, prepernicious stage occurs quite frequently in pernicious anemia. Further observations and investigations may be in a position to find out the frequency of such a prepernicious stage. It may be, that its onset depends on the speed with which deficiency of the gastric secretion develops, producing the prepernicious iron-deficiency stage by slow gradual evolution of gastric insufficiency. Maybe the relatively quick onset of complete achlorhydria results in the development of pernicious anemia without a prepernicious phase. The third possibility is, that deficiency of gastric secretion with achlorhydria remains stationary and causes hypochromic iron-deficiency anemia. Instances of this phenomenon may occur at any age and are nothing out of the ordinary. Constitutional factors probably play an important part in the mode of onset of the three forms of anemia. Damage to the gastric mucosa frequently is much more extensive than thought at first. More cases of hypochromic iron-deficiency anemia passing into pernicious anemia may be discovered, if follow-up observations are carried on long enough.

The case is also a contribution to the problem of the achrestic anemia. The increase of the tissue basophile cells is perhaps a sign of the marrow intoxication, which is the cause of the failure of the liver therapy.

Literatur.

Literatur (soweit sie nicht in Fussnoten angeführt): Leitner, St. J.: Die intravitale Knochenmarksuntersuchung. Die Hämatologie im Lichte der Sternalpunktion. Basel, B. Schwabe 1945. — Englische Ausgabe: Ed. Churchill 1948 (im Druck).

both fluorine and arsenic. Any fluorine or arsenic found in the specimens of the nails would, therefore, represent an average amount excreted over the number of years during which the nail clippings have been collected. The cuttings of the hair, on the other hand, were collected ad hoc on 2 different occasions and kept separate, so that any content of either fluorine or arsenic found in them would correspond to the limited periods of time only, during which these noxa may have been ingested. This procedure of independent duplication of analysis by 2 laboratories was adopted in the hope that some useful information might emerge, and also with a view to checking the reliability of the methods employed for the quantitative fluorine determination. Strong doubts concerning this reliability have already been expressed on previous occasions (Cristiani & Gautier, 1925; Churchill, 1932; McClure, 1933; Spira, 1943, 1946 b).

The following are the results of the respective analyses:

(1) *Royal Army Medical College, Millbank, S.W. 1.*

Report by Colonel L. S. Stott, Professor of Hygiene:

The nail cuttings contained 6.5 micrograms of fluorine per gramme, and 1.0 microgram of arsenic per gramme (*i. e.* parts per million).

Report by Colonel T. F. Kennedy, Professor of Hygiene:

The sample of hair contained:

(a) Arsenic, 0.25 part As_2 per million.

(b) Fluorine, 0.09 part F_2 per million.

As the proportion of fluorine appears to be very low, it is recommended that a further sample be submitted in due course, in order to check the result. There does not appear to be any report in the literature on the proportion of fluorine in hair.

Accordingly, a sample of hair cut on a subsequent occasion was submitted for analysis. The following is the result (Colonel T. F. Kennedy, Professor of Hygiene):

Repeat sample of hair contains fluorine 1.6 p.p.m.

(2) *The Clinical Research Association Ltd., W.C. 2.*

Report by Dr R. S. Ralph, Laboratory Director:

The total weight of the nail cuttings is 5.4 grammes.

On analysis the following results were obtained:

Fluorine	24.03 p.p.m.
Arsenic (As_2O_3)	0.25 p.p.m.

or, expressed in milligrams in the total weight

Fluorine	0.130 mg
Arsenic	0.00135 mg

The total weight of the specimen of hair is 3.30 grammes. Analysis yielded the following results:

Fluorine	1.16 p.p.m.
Arsenic (As_2O_3)	0.61 p.p.m.

or, expressed in milligrams in the total weight of the specimen

Fluorine	0.0038
Arsenic (As_2O_3)	0.0020

The frequent, but not accounted for, occurrence of arsenic in the tissues of persons who have never been exposed to any of the known risks of intoxication led to the convenient conclusion that it is a natural constituent of the human body. It will, however, be remembered that, even in cases of chronic arsenical poisoning, the interpretation of the results of chemical analysis is by no means uniform. According to Bamford (1940), in one case the quantity of 15.5 mg of arsenic detected in the viscera was deemed insufficient to account for death; in another, no arsenic could be found, but the ante-mortem features of the disease tipped the scales in favour of a verdict of murder.

In a fatal case of arsenical poisoning described by Glaister (1945), the post-mortem examination of the finger- and toe-nails revealed between 46 p.p.m. and 64 p.p.m. of arsenic; in the hair, amounts ranging from 3.3 p.p.m. to 10 p.p.m. of arsenic were found. In 9 persons, on the other hand, all of whom were laboratory workers, the average arsenic content of the nail clippings was 8 p.p.m., and 21 specimens of hair from various patients who died from causes other than arsenical poisoning, contained on the average 0.72 p.p.m. of arsenic. Compared with all these results of analysis, the much smaller quantities found in the present case (1 p.p.m. and 0.25 p.p.m. respectively in the nail clippings, and 0.25 p.p.m. and 0.61 p.p.m. respectively in the hair cuttings) thus rule out the possibility that arsenic is the sole aetiological factor in the disease picture, and help to reject the clinical diagnosis of chronic arsenical poisoning.

Amongst the halogens, fluorine is reputed to have the highest toxicity. The protracted ingestion of as little as 0.1–0.15 mg per kg of body weight per day has been found (DeEds, 1933; Greenwood, 1940) sufficient to produce mottled teeth as an external manifestation of fluorosis in experimental animals.¹ McClure (1939) has calculated that an average child of 15 kg, equal to 33 lbs., living in a mottled enamel area whose drinking water contained 2 to 3 p.p.m. of fluorine would ingest 0.15 mg–0.30 mg fluorine per kg body weight a day.² The action of fluorine is cumulative, and, in the present case, the amounts of 6.5 p.p.m. and

¹ 0.1–0.15 mg per kg is equal to 1/1200–1/800 grain per lb.

² 0.15 mg–0.30 mg per kg is equal to 1/800–1/400 grain per lb.

24.03 p.p.m. respectively found in the finger- and toe-nails, and 0.09 p.p.m., 1.6 p.p.m., and 1.16 p.p.m. respectively detected in the specimens of hair, large though they are, must be considered as representing only a fraction of the poison accumulated in the body. *Intra vitam*, the presence of fluorine in the keratin tissues has no doubt diagnostic significance. Velu (1932) states that, just as in the case of arsenic, copper, etc., the ectodermal tissues (hair, nails, epidermis) would be the natural channels of the excretion of fluorine, thus explaining the accumulation of the element in these organs. McClure (1933), too, quotes Gautier & Clausmann as well as Brandl & Tappeiner for the statement that the accumulation of fluorine in the hair, nails and epidermis represents a means of fluorine excretion. In some fatal illnesses of obscure nature, a routine post-mortem chemical search for the presence of fluorine in the organs, especially the liver, kidneys, brain, spleen and muscles, may in some cases help to explain the cause of death.

Since the actions of fluorine and arsenic appear to be practically identical, it becomes obvious that, in cases in which both substances are found to be present simultaneously, their aggregate amount will produce a more pronounced effect than would any one of them alone in the quantity hitherto ingested for any length of time.

The occurrence of mottled teeth has thus far been used to determine the incidence of fluorosis, and attributed to the ingestion of fluorine contained only in the drinking water. Since, however, signs and symptoms of chronic fluorine poisoning, including mottled teeth, have been frequently found also in areas whose drinking water was practically free from fluorine, it became evident that the noxon would have to be searched for in various articles of food. Cutting off food prepared in aluminium cooking utensils, in addition to other measures directed against fluorosis, has been clinically found to alleviate several signs and symptoms of the disease. It will be remembered that, in the production of the aluminium metal, the fluorine mineral cryolite, Na_2AlF_6 (or $3\text{NaF} \cdot \text{AlF}_3$), is an essential raw material.

To determine whether the small quantities of arsenic frequently found in the nails and hair of people who were never exposed to the risk of intoxication should be considered as a «natural» constituent of the body, or whether they might be due to any arsenic contained in some suspected articles of food in association with

ELIMINATION OF FLUORINE.

fluorine, the method applied in the case of the nails and hair has again been employed, that is to say, specimens were submitted for analysis for both fluorine and arsenic, the examination of some of them being duplicated independently in different laboratories. Apart from a few chemical substances used for sedimentation, filtration and sterilization of drinking water, only articles were selected for analysis which formed an important part in the average person's food consumed in everyday life. The following are the results of the investigation:

(1) *Royal Army Medical College, Millbank, S.W. 1.*

Report by Colonel T. F. Kennedy, Professor of Hygiene:

Sample labelled »Tap water» contained:¹

Fluorine 0.86 p.p.m.

Arsenic under 0.02 p.p.m.

Sample labelled »Tea»:²

Fluorine 2.08 p.p.m.

Arsenic 0.01 p.p.m.

Sample labelled »Beer. Jenner's Golden Ale»:¹

Fluorine 0.8 p.p.m.

Arsenic 0.05 p.p.m.

Soup made of Symington's soup powder (Ox-tail):²

Fluorine 5.5 p.p.m.

Arsenic under 0.01 p.p.m.

Symington's soup powder (Ox-tail):

Fluorine, duplicate determinations both yielded 4.0 p.p.m.

Arsenic 0.5 p.p.m.

Two samples of Symington's soup powder (Celery) contained:

Fluorine 1.5 p.p.m. and 1.0 p.p.m. respectively.

Arsenic 0.1 p.p.m. and less than 0.1 p.p.m. respectively.

Symington's soup powder (Hare):

Fluorine 2.5 p.p.m.

Arsenic 0.2 p.p.m.

Report by Major Stanley Elliott, Analytical Chemist:

Symington's soup powder (Kidney):

Fluorine 5 p.p.m.

Arsenic 0.1 p.p.m.

Symington's soup powder (Mock Turtle):

Fluorine 1 p.p.m.

Arsenic 0.05 p.p.m.

Symington's soup powder (Mulligatawny):³

Fluorine 0.75 p.p.m.

Arsenic 0.1 p.p.m.

¹ See footnote p. 86.

² See footnote p. 87.

³ See footnote p. 88.

Symington's soup powder (Pea):¹

Fluorine 0.75 p.p.m.

Arsenic 0.2 p.p.m.

Symington's soup powder (Tomato):¹

Fluorine 1 p.p.m.

Arsenic 0.4 p.p.m.

Report by Colonel T. F. Kennedy, Professor of Hygiene:

Sample of 17/18 % Kibbled S/Alumina, Peter Spence & Sons Ltd:

Fluorine 2.4 p.p.m.

Arsenic 0.4 p.p.m.

Sample of commercial Lump Alum, Peter Spence & Sons Ltd.:

Fluorine less than 0.1 p.p.m.

Arsenic nil.

Sardinhas Portuguesas em oles. Marca Nacional:

Fluorine 15.6 p.p.m.

Arsenic 2.0 p.p.m.

In view of the comparatively large amount of arsenic in the sardines, there is an interesting article by A. Chaston Chapman in the Analyst 1926, p. 548, stating that amounts of arsenic in excess of the standard of 1/100 grain per pound were found in crustacea and shell fish. The high proportion of fluorine is very interesting, and there appear to be no references to it in the literature.

Buns, not labelled with name of baker:

Fluorine 1.2 p.p.m.

Arsenic less than 0.2 p.p.m.

SDI Lemon Squash. Dilute to taste L 135:

Fluorine 0.15 p.p.m.

Arsenic 0.03 p.p.m.

SDI Orange Squash. Dilute to taste L 135:

Fluorine 0.28 p.p.m.

Arsenic 0.06 p.p.m.

Cooking fat, not labelled with name of manufacturer:

Fluorine 1.8 p.p.m.

Arsenic 0.6 p.p.m.

Margarine, not labelled with name of manufacturer:

Fluorine less than 0.1 p.p.m.

Arsenic 0.8 p.p.m.

Cigarettes labelled »K 4's Kensitas« were burnt and the smoke analyzed for fluorine and arsenic.

Twelve cigarettes yielded sixteen thousandths (0.016) of a milligramme of fluorine, and four thousandths (0.004) of a milligramme of arsenic.

Report by Major Stanley Elliott, Analytical Chemist:

Stellafilt Filtering Powder, The Paterson Engineering Coy. Ltd., Kingsway, W.C. 2.

Fluorine 68 p.p.m.

Arsenic 0.6 p.p.m.

¹ See footnote p. 88.

Alag Metasil Filter Bed Charge. The Metafiltration Co. Ltd. Belgrave Road, Hounslow, Middx., England:

Fluorine 120 p.p.m.

Arsenic 1.4 p.p.m.

Water Sterilizing Powder (Chlorine 25 per cent.) I.C.I. (General Chemicals) Ltd. Greenbank Works, Widnes, England:

Fluorine 39 p.p.m.

Arsenic 0.4 p.p.m.

Fertilizer (Lime), as used at Arborfield, Berks.:

Fluorine 404 p.p.m.

Arsenic less than 0.1 p.p.m.

Sainsbury's Pure Coffee. J. Sainsbury, Stamford House, London S.E. 1.

Fluorine 0.7 p.p.m.

Arsenic less than 0.1 p.p.m.

Crosbie's Damson Jam, Crosbie's Pure Food Co. Ltd. Bradley, Lines. and Southall, Middx., England. Fresh Fruit Standard:

Fluorine 0.3 p.p.m.

Arsenic less than 0.1 p.p.m.

Bisto for gravy. Manufactured by Cerebos Ltd., London, N.W. 10.

Fluorine 5.5 p.p.m.

Arsenic less than 0.1 p.p.m.

Bospur Gravy Powder, Bospur, 246, Banner Street, London, E.C. 1.

Fluorine 0.5 p.p.m.

Arsenic 0.2 p.p.m.

Oxo cubes:

Fluorine 1.7 p.p.m.

Arsenic 0.3 p.p.m.

Australian Bartlett Pears. S. P. C. Brand, The Shepparton Fruit Preserving Co. Ltd. Shepparton, Victoria, Australia:

Fluorine 0.15 p.p.m.

Arsenic 0.15 p.p.m.

Saxa Table Salt. Saxa Salt Co, Greatham, England:

Fluorine less than 0.1 p.p.m.

Arsenic 0.6 p.p.m.

Tate and Lyle Granulated Sugar:

Fluorine less than 0.1 p.p.m.

Arsenic approx. 0.05 p.p.m.

Bird's Custard Powder, Alfred Bird & Sons Ltd. Devonshire Works, Birmingham:

Fluorine 0.3 p.p.m.

Arsenic less than 0.1 p.p.m.

Chivers Jelly, Greengage:

Fluorine 0.1 p.p.m.

Arsenic 0.5 p.p.m.

Barley Flakes. J. Sainsbury, Stamford House, London, S.E. 1.

Fluorine 0.1 p.p.m.

Arsenic 0.2 p.p.m.

Viota Caramel Flavour Cake Mixture. Manufactured by Stoddart and Hanford Ltd., 7, Islington Green, N. 1.:

Fluorine 0.3 p.p.m.

Arsenic 0.2 p.p.m.

Selsa Vanilla Chocolate. Sold only by J. Sainsbury, Stamford House, London, S.E. 1:

Fluorine 0.2 p.p.m.

Arsenic less than 0.1 p.p.m.

Cadbury's Bournville Cocoa, Cadbury, Bournville:

Fluorine 0.5 p.p.m.

Arsenic 0.3 p.p.m.

Macaroni. J. Sainsbury, Stamford House, London, S.E. 1:

Fluorine 0.3 p.p.m.

Arsenic less than 0.1 p.p.m.

Semelina. J. Sainsbury, Stamford House, London, S.E. 1:

Fluorine 0.5 p.p.m.

Arsenic 0.3 p.p.m.

Mixed sweets, some unlabelled, others »Bensons Toffee», »Dulcete Confections» and »Paseall». Mean of mixture of sweets:¹

Fluorine 1.55 p.p.m.

Arsenic 0.15 p.p.m.

Colonel T. F. Kennedy, Professor of Hygiene, reports that the standard method (perchloric acid) of the Society of Public Analysts was employed for the fluorine determinations, and the quantitative Gutzeit method for that of arsenic. The smoke of burnt cigarettes was analyzed by air being drawn slowly through the lighted cigarettes, then the products of combustion passed through water, and the arsenic and fluorine determined in the water.

(2) *The Clinical Research Association Ltd., London, W.C. 2.*

Report by Dr. R. S. Ralph, Laboratory Director:

Specimen 1 bottle Drinking Water marked.² Analysis yielded the following results:

Fluorine 0.98 p.p.m.

Arsenic nil.

Specimen 6 $\times \frac{1}{2}$ pint bottles Beer marked. The contents of the six half-pint bottles were mixed and treated as one sample.³ Analysis yielded the following results:

Fluorine 0.54 p.p.m.

Arsenic (As_2O_3) 0.13 p.p.m.

The amount of arsenic found is small, being less than the limit suggested by the Royal Commission on Arsenical Poisoning 1903 (0.14 p.p.m. or one-hundredth grain per gallon).

¹ See footnote p. 88.

² This specimen came from the same tap and on the same occasion as that described on p. 83.

³ This specimen of beer was identical with that described on p. 83.

Specimen 1 bottle of Tea marked (Tea Infusion):¹ Analysis yielded the following results:

Fluorine 1.92 p.p.m.

Arsenic nil.

Assuming that the infusion was made by adding about one-third of an ounce (equal to 9.5 g) of tea to a pint (equal to 0.568 litre) of water, the amount of fluorine present in the dry tea would not exceed 129 p.p.m., and many analyses have shown that this is quite an ordinary amount to find in tea.

Specimen 1 bottle of Soup marked:² Analysis yielded the following results:

Fluorine 2.36 p.p.m.

Arsenic (As_2O_3) 0.2 p.p.m.

Specimen Soup (Celery) marked Symington's soup powder. Analysis yielded the following results:

Fluorine 1.64 p.p.m.

Arsenic nil.

Specimen soup powder (Hare) marked Symington's:

Fluorine 2.78 p.p.m.

Arsenic nil.

Specimen Symington's powdered soup (Ox-tail):

Fluorine 3.80 p.p.m.

Arsenic (As_2O_3) 0.73 p.p.m.

Specimen Symington's soup powder marked (Mock Turtle):

Fluorine 3.06 p.p.m.

Arsenic (As_2O_3) 0.20 p.p.m.

Specimen Symington's soup powder (Kidney):

Fluorine 1.08 p.p.m.

Arsenic (As_2O_3) 0.25 p.p.m.

According to information obtained from Dr. R. S. Ralph, the reagents used in the estimation of fluorine were of Analar quality, and of the AsT quality in the case of arsenic estimation (British Drug Houses Ltd).

The methods used were:

Arsenic — as given in the pamphlet entitled »Determination of Arsenic in Foodstuffs contaminated by arsenical War Gases» issued under the auspices of the Society of Public Analysts.

Fluorine — as given in »The Determination of Fluorine in Foods», a report of the Sub-Committee of the Analytical Methods Committee; published by the Authority of the Council as a Stan-

¹ This specimen was part of the infusion, from which another sample has shown on a previous analysis to contain fluorine 2.08 p.p.m. and arsenic 0.01 p.p.m. (see p. 83).

² This specimen was collected from the cooking utensil at the same time as the specimen which on a previous analysis has shown to contain 5.5 p.p.m. of fluorine and under 0.01 p.p.m. of arsenic (see p. 83).

standard method of the Society of Public Analysts (see also Analyst 1944, page 243).

(3) With a view to extending the list of articles of food for a duplicated analysis for both fluorine and arsenic, I invited the help of the Medical Officer of Health for the Borough of Hampstead (Dr. H. L. Oldershaw). The following is the report of the analysis carried out by Dr. H. E. Cox, Public Analyst and Consulting Chemist:

Pea Soup Powder, Tomato Soup Powder, Mulligatawny Soup Powder¹ — All these samples are genuine and satisfactory. The soup powders did not contain any fluorine. We found no arsenic at all in the samples of the Tomato Soup Powder and Mulligatawny Soup Powder. The sample of Pea Soup Powder contained 0.7 p.p.m. of arsenic, which is insignificant. Analysis of Sardinhas Portuguesas em oleo. Marca Nacional, of Oxo Cubes, and of Chocolates² revealed that all these samples are genuine and free from arsenic and fluorine.

Inquiry into the methods of analysis used elicited the following information from Dr. H. E. Cox:

Arsenic was determined by the Gutzeit test. The determination of fluorine is rather difficult, and is carried out by a method standardized by the Society of Public Analysts (Analyst 1944, 69, 243) and consists in the distillation of the material, after ashing, with perchloric acid; and the fluorine in the distillate is determined by means of thorium nitrate and alizarine-sulphonic acid.

Determination of Fluorine and Arsenic in Parts per Million (p.p.m.).

Article	R.A.M. College, Millbank, S.W. 1		Clinical Research Assoc. Ltd., W.C. 2		Dr. H. E. Cox, E.C. 3	
	F	As	F	As	F	As
Finger and toe-nails	6.5	1.0	24.03	0.25		
Hair	(a) 0.09	a 0.25	1.16	0.61		
	(b) 1.6	b) not determined				
Drinking Water	0.86	under 0.02	0.98	NIL		
Tea infusion	2.08	0.01	1.92	NIL		
Beer (Jenner's Golden Ale)	0.8	0.05	0.54	0.13		
Soup, made of Symington's soup powder						
(Ox-tail)	5.5	under 0.01	2.36	0.2		

¹ All these samples were of the same manufacture (Symington's) as were those examined on a previous occasion (see pp. 83 and 84).

² The «Chocolates» were of the same quality, and obtained in the same sweet-shop, as were the «mixed sweets» examined on a former occasion (see p. 86).

Article	R.A.M. College, Millbank, S.W. 1		Clinical Research Assoc. Ltd., W.C. 2		Dr. H. E. Cox, E.C. 3	
	F	As	F	As	F	As
Symington's soup powder (Ox-tail)	4.0 duplicate deter- mination	0.5	3.80	0.75		
Symington's soup powder (Celery)	(a) 1.5 (b) 1.0	(a) 0.1 (b) less than 0.1	1.64	NIL		
Symington's soup powder (Hare)	2.5	0.2	2.78	NIL		
Symington's soup powder (Kidney)	5.0	0.1	1.08	0.25		
Symington's soup powder (Mock Turtle)	1.0	0.05	3.06	0.20		
Symington's soup powder (Mulligatawny)	0.75	0.1			NIL	NIL
Symington's soup powder (Pea)	0.75	0.2			NIL	0.7
Symington's soup powder (Tomato)	1.0	0.1			NIL	NIL
Sardinas Portuguesas em oles. Marca Nacio- nal	15.6	2.0			NIL	NIL
Oxo Cubes	1.7	0.3			NIL	NIL
Mixed Sweets, some un- labelled, others »Ben- sons Toffee», Dulcete Confections Ltd., »Pas- call». Mean of mixture of sweets	1.55	0.15			NIL	NIL
Commercial Lump Alum. Peter Spence & Sons Ltd.	less than 0.1	NIL				
17/18 % Kibbled S/Alu- mina. Peter Spence & Sons Ltd.	2.4	0.4				
Water Sterilizing Powder (Chlorine 25 per cent). I.C.I. (General Chemi- cals) Ltd., Greenhawk Works, Widnes, Eng- land	39	0.4				
Stellafilt Filtering Pow- der. The Paterson En- gineering Co., Ltd., Kingsway, London ...	68	0.6				
Alag Metasil Filter Bed Charge. The Metafiltra- tion Co., Ltd., Belgrave Road, Hounslow, Mid- dlesex, England	120	1.4				

Article	R.A.M. College, Millbank, S.W. 1		Clinical Re- search Assoc. Ltd., W.C. 2		Dr. H. E. Cox, E.C. 3	
	F	As	F	As	F	As
Fertilizer (Lime) as used at Arborfield, Berks...	404	less than 0.1				
Buns, not labelled with name of baker	1.2	less than 0.2				
S.D.I. Lemon Squash. Dilute to taste L. 135 .	0.15	0.03				
S.D.I. Orange Squash. Dilute to taste L. 135 .	0.23	0.06				
Cooking fat, not labelled with name of manufac- turer	1.8	0.6				
Margarine, not labelled with name of manufac- turer	less than 0.1	0.8				
Sainsbury's Pure Coffee. J. Sainsbury, Stamford House, London, S.E. 1	0.7	less than 0.1				
Crosbie's Damson Jam, Crosbie's Pure Food Co. Ltd., Bradley, Lines. & Southall, Middlesex, England. Fresh Fruit Standard	0.3	less than 0.1				
Bisto for Gravy. Manu- factured by Cerebos Ltd., London	5.5	less than 0.1				
Bospur Gravy Powder, Bospur, 246, Banner Street, London, E.C. 1	0.5	0.2				
Australian Bartlett Pears, S. P. C. Brand, The Shepperton Fruit Pre- serving Co., Ltd., Shep- perton, Victoria, Au- stralia	0.15	0.15				
Saxa Table Salt, Saxa Salt Co., Greatham, England	less than 0.1	0.6				
Tate & Lyle Granulated Sugar	less than 0.1	approx. 0.05				
Bird's Custard Powder, Alfred Bird & Sons, Ltd., Devonshire Works, Birmingham...	0.3	less than 0.1				

Article	R.A.M. College, Millbank, S.W. 1		Clinical Research Assoc. Ltd., W.C. 2		Dr. H. E. Cox, E.C. 3	
	F	As	F	As	F	As
Chivern Jelly, Greengage	0.1	0.5				
Barley Flakes, J. Sainsbury, Stamford House, London, S.E. 1	0.1	0.2				
Viota Caramel Flavour Cake Mixture. Manufactured by Stoddard & Hanford Ltd., 7, Islington Green, N. 1	0.3	0.2				
Selsa Vanilla Chocolate. Sold only by J. Sainsbury, Stamford House, London, S.E. 1	0.2	less than 0.1				
Cadbury's Bournville Cocoa. Cadbury, Bournville	0.5	0.3				
Macaroni. J. Sainsbury, Stamford House, London, S.E. 1	0.3	less than 0.1				
Semolina. J. Sainsbury, Stamford House, London, S.E. 1	0.5	0.3				
Cigarettes, labelled K. 4's Kensitas		Twelve cigarettes yielded sixteen thousandths (0.016) of a milligram of fluorine and four thousandths (0.004) of a milligram of arsenic				

For the sake of easier visualization and comparison, the independent results obtained are given in a tabular form. A glance at this table reveals that the findings are more consistent in the determination of arsenic than in the estimation of fluorine. This may be partly due to the fact that the methods of estimating even minute doses of arsenic are very delicate, whereas the method of quantitative determination of fluorine does not seem to have reached the same stage of perfection. It is suggested that, to settle the long-standing controversy concerning the question of whether arsenic is a natural constituent of the body, the small quantities found in various articles of food should be given due consideration. It is only as a result of the legislation introduced in

this country following the findings and recommendations of the Royal Commission which was set up in 1903 in connexion with the Manchester epidemic of arsenical poisoning, that the quantities of arsenic found in various articles of food are now kept within narrow limits. It is submitted that the small amounts of arsenic contained in these articles of food fully account for the presence of the noxon in the nails and hair even of those cases which do not exhibit any obvious signs and symptoms. Thus the theory that arsenic is a natural constituent of the body appears not to be tenable.

In the case of fluorine determination, I have it on the authority of Major Stanley Elliott of the Royal Army Medical College that, amongst the pitfalls encountered, a grave error may arise if the technical perchloric acid is used as a reagent, instead of the chemically pure material, since it may itself contain fluorine as an impurity. The discrepancy in the results obtained from the 2 laboratories for the finger- and toe-nails (6.5 p.p.m. against 24.03 p.p.m.) is all the more striking as the two samples were taken out of a collection in which nails with a possibly large fluorine content were mixed with those of a fluorine content which may have been low. To a lesser extent there is also inconsistency in the findings obtained for the samples of the drinking water, the tea infusion, and, more especially, the soup made of Symington's soup powder (ox-tail). All these samples were collected in my presence: the bottles of drinking water were filled from the same tap and on the same occasion, one immediately after the other; the tea infusion came from the same pot first into one bottle, then into the second; and the soup was poured first into one collecting bottle, then into the second, from the cooking utensil in which it was prepared to be consumed by many people.

A more pronounced inconsistency in the results of the determination of fluorine was revealed by the fact that none of the 6 samples analyzed by Dr. H. E. Cox was found to contain it, although other samples of identical articles examined elsewhere were contaminated to an appreciable extent. Since the same applies also to the results obtained by him for the estimation of arsenic in all but one sample (the arsenic content in the one sample being even in excess of that detected elsewhere in another specimen of the same article), the possibility must be borne in mind that neither fluorine nor arsenic may perhaps, after all, be invariably present as an impurity in equal quantities in every sample of the same

article. If this is true, it becomes apparent that, in some as yet unexplained manner, these noxa may have found their way into some samples of any article of food but not into others.

There is also a striking discrepancy between the fluorine content in the filtering and sterilizing substances employed in the process of purification of the water, on the one hand (39 p.p.m., 68 p.p.m. and 120 p.p.m. respectively), and the amounts of fluorine commonly found in the drinking water itself after its purification has been completed, on the other. The latter represent only a fraction of the former, and the question of what has happened to the bulk of the fluorine employed in the course of the purifying process awaits elucidation. DeEds (1933) states that »upon contact of fluorine with water ozone is evolved and hydrofluoric acid formed», and Spira (1943) concludes from his results of analysis of gradually increasing concentrations of fluorine in distilled water that »the amount of fluorine present in any suspension is perhaps only partly dissolved, another part being free and able to escape in a volatile form».

Nor must the long list of articles of our daily food containing variable quantities of fluorine be disregarded. None of them is found to be quite free of the noxon, which is known to be present also in vegetables grown in a soil with an added chemical fertilizer. The sample of fertilizer, personally collected on a farm, has been found to contain 404 p.p.m. of fluorine. Cattle are affected by chronic fluorine poisoning when grazing on a pasture containing fluorine as a natural constituent, as is the case, for example, in North Africa (Velu, 1932), or on a pasture contaminated by the addition of rock phosphate as fertilizer. Epidemics of fluorosis amongst cattle and people living on farms in the vicinity of aluminium works (Cristiani & Gautier, 1925, 1926 a, b, c; Boddie, 1945) and of brickworks (Discussion, 1941), as well as those occurring in association with calcining of ironstone (Green, 1946), have been recorded. In all these cases the pastures and the atmosphere were contaminated by hydrofluoric acid emanating from the works. From the point of view, however, of both Preventive Medicine and Forensic Medicine, it is of paramount interest to realize that, like arsenic, fluorine is being increasingly used as an insecticide and preservative in a great variety of articles of food, mainly as cryolite (Na_3AlF_6) and barium fluosilicate (BaSiF_6). The danger arising from this source has been pointed out by several writers (McClure, 1933; Smith, Lantz & Smith,

prescribed for arsenic, the toxicity of both noxa being practically identical.

I wish to express my thanks to all those who have helped in the course of this investigation. I am, in particular, grateful to Colonel T. F. Kennedy for permission to have the numerous analyses carried out at the Laboratories of the Royal Army Medical College, and to Major Stanley Elliott, Analytical Chemist, for the courtesy of performing the large number of estimations. Mr. B. J. D. Warren, the Chief Sanitary Inspector for the Frimley and Camberley Urban District, Surrey, kindly arranged the duplication of some of the analyses.

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Hormone of Rest.

By

Professor Doctor NINA MEDWEDEWA,

Corr. Member of the Academy of Sciences of the U. S. S. R.

(Submitted for publication January 2, 1946.)

An active principle is extracted from a triturated adrenal cortex by means of acidulated water. This substance plays a very important rôle in the regulation of carbohydrate metabolism chiefly in its synthetic-anabolic phase. It is precipitated from the extract by means of sodium stearate. We have called this substance »corticaline».

It produces a marked fall in the blood sugar content on parenteral administration. During the height of corticaline hypoglycemia sometimes only traces of sugar may be found in the blood. In contrast to insulin hypoglycemia corticaline hypoglycemia is never followed by convulsions or by any other manifestations of intoxication. This is one of its characteristic features.

This substance which may be extracted from the adrenal cortex by means of acidulated water and may then be absorbed from the extract by means of sodium stearate, is a specific product of adrenal cortex. It can be extracted from no other organs even by the same methods of extraction and isolation. Thus hypoglycemia cannot be produced by similarly obtained extracts, of the liver, the stomach, the lungs, the intestine, the pituitary, the pancreas, the lymphatic tissue, and of cancerous tissue. And a similarly obtained muscle preparation produces not hypoglycemia, but hyperglycemia.

Corticaline is a true hormone. It is therefore devoid of type specificity. Extracts obtained from the adrenal cortex of an ox, a sheep, a pig produce their characteristic reactions in a dog,

a mouse, a cat and a rat. The adrenal cortex even from very remote species of animals gives the same active extract. Thus corticaline obtained from the adrenal cortex of a Mediterranean Sea shark produces a typical hypoglycemic reaction in a rabbit.

Corticaline cannot be obtained from the pancreas. Consequently it cannot be regarded as absorbed or deposited insulin. And conversely: no active preparation of insulin can be obtained from adrenal cortex by means of any of the methods used for insulin isolation. Thus the two hypoglycemia producing hormones — insulin and corticaline — are of a different chemical nature.

The action of corticaline is independent of the pancreas: its characteristic action is also observed in depancreatized animals during different stages of diabetes.

Thus this adrenal cortex hormone 1) is specific for the adrenal cortex activity, 2) is independent of the hypoglycemizing effect of the pancreatic hormone and 3) is independent of the species of animals.

The mechanism of the physiological corticaline action consists in an increase of the synthetic reparative processes concerned in carbohydrate metabolism.

Our numerous investigations performed on different animals by means of different experimental methods allow us to assert that the catabolic phase of metabolism is not increased under corticaline influence *i. e.* that the cause of the fall in blood sugar is neither its decomposition nor its increased oxidation. In the first case some products of the decomposition would be found in superfluity in the tissues, in the blood or in the urine of corticallinised animals — namely non-nitrous carbonic compounds, as residue carbonic compounds in tissues, lactic acid and ketone bodies in blood and not completely acidified carbonic compounds in urine.

The content of non coagulating carbonic compounds in the tissues is not increased after corticaline administration, in most of the organs it is even decreased. Thus the chrome indexes is reduced from 1.51 to 1.16 in the kidneys, from 1.59 to 1.24 in the brain, from 1.39 to 1.02 in the skeletal muscles and from 1.76 to 1.6 in the intestine.

The excretion of carbonic compounds by the kidneys is also reduced. In normal dogs fed in the ordinary way the carbonuric quotient of the urine was found to be 0.72 on the average; it was reduced to 0.50 after corticaline administration.

The content of lactic acid and ketone bodies in blood is not increased under corticoline influence; that indicates that the rate of glycolysis is not increased either.

The glycolysis in tissues isolated from corticalinised animals just as the glycolysis in tissues placed in a corticoline containing medium is less intensive than the glycolysis of the same tissues under the same conditions but without corticoline administration.

Thus the estimations of the chrome index, of the carbonuria, of the lactacidemia, acetonemia, of the glycolysis in tissues of corticalinised animals and in tissues placed in a corticoline containing medium indicate that corticoline limits the glycolytic phase of carbohydrate metabolism.

Corticoline reduces also the sugar combustion. The gaseous exchange is as a rule also diminished after corticoline administration. A control rat excretes on the average 337 mg CO₂ per kg/h, after corticoline administration it only excretes 224 mg. This corticoline action is a specific one, as is also its influence on hypoglycemia. A similarly obtained pituitary extract exerts an opposite influence; the gaseous exchange is augmented on the average from 375 to 833 mg per kg/h.

While the glycolytic and the respiratory phases of the metabolism are restricted under corticoline influence, the synthetic phase is considerably augmented. I will describe here some of my observations of the corticoline action on the synthesis of the principal energetic and dynamogenic compounds — namely glycogen, creatine phosphate and hexose phosphate: The corticoline influence is very marked under normal conditions of metabolism, but it is still more marked during muscle work performed under conditions of adrenal insufficiency *i. e.* when there is an increased demand and diminished possibilities.

Glycogen.

The glycogen content in the tissues of normal animals is increased after corticoline administration. Thus the concentration of glycogen in the liver of a rat increases from 531 to 1065 mg per cent; in other words it is doubled. It is also doubled in the muscles of a normal rat, increasing on the average from 259 to 469 mg per cent. In the organs of a normal rabbit the glycogen concentration is also increased: in the liver from 1139 to 1608 mg per cent, in the kidneys from 419 to 817 mg per cent, in the intestine from

591 to 792 mg per cent; in skeletal muscles from 490 to 795 and in the brain from 693 to 845 mg per cent.

Especially marked is the corticoline influence on the glycogen synthesis during muscle work. It is a well known fact that glycogen storage breaks down during muscle work. In a mouse even during moderate muscle work the glycogen concentration in the liver is more than halved during an hour (from 580 to 210 mg per cent on the average). The glycogen content of the liver recovers gradually and slowly during repose. But if before work corticoline is administered, the restoration of the used up glycogen goes on so quickly that the glycogen concentration of the liver taken immediately after muscle work is not diminished as can be seen in the control mouse, but is it even increased in comparison with the glycogen concentration in the liver of a resting mouse. Thus after corticoline administration the disappearance of the liver glycogen is compensated by its immediate resynthesis.

In the muscle of a normal animal during moderate work the resynthesis of the used up glycogen takes place so quickly that its concentration is even increased. It is still more increased during repose after work. Thus the average glycogen concentration in the muscle of a resting mouse is 250 mg per cent; immediately after muscle work — 370 mg per cent, and after repose — 440 mg per cent. Corticoline does not change this process in the main; but the glycogen concentration in the muscle of a mouse 1) in rest, 2) immediately after work and 3) after repose is in a corticalinised animal higher than in a normal one. Thus the influence of corticoline in regard to the muscles is the same as in regard to the liver — namely: the resynthesis of the glycogen used up during work.

The process of resynthesis is severely disturbed in adrenal insufficiency. The liver of an adrenalectomised animal loses its glycogen storage during work and it is not restored during repose. After repose the glycogen concentration in the liver is on the same low level as it is in the liver of a fatigued animal. But if before muscle work corticoline is administered to an adrenalectomised animal the resynthesis of glycogen lost during work takes place so quickly and so completely that: in the liver taken immediately after work the glycogen concentration is the same as in the liver of a resting animal and two and a half times more than in the liver of an adrenalectomised animal to which corticoline was

not administered. Thus corticaline compensates the insufficiency of the resynthesis caused by adrenalectomy.

The influence of corticaline is the same on the glycogen synthesis in the muscles of an adrenalectomised animal. The muscle as well as the liver loses its capacity for resynthesis after adrenalectomy. In a normal animal there takes place restoration of the glycogen used up during moderate muscle work: in an adrenalectomised animal the muscle is incapable of this restoration. But after corticaline administration the resynthesis returns to the normal: the glycogen content is not only decreased but is even increased in comparison with its content in a resting muscle. Just as in a normal animal this glycogen concentration also remains increased after repose following work. Thus the disturbance of the reparative phase of metabolism in the muscle caused by adrenalectomy is restored by means of corticaline just as in the liver.

Phosphagen.

Corticaline aids the synthesis of the creatine ether of phosphoric acid. After corticaline administration to the normal rabbit the phosphagen content, as may be seen from the given quantitative data, is increased in all studied organs — in the heart, the liver, the kidneys, in the intestine, skeletal muscles and the brain.

The creatine phosphate phosphorus concentration (in mg per cent).

	Heart	Liver	Kidney	Intestine	Muscle	Brain
Control animal.....	7.4	3.9	4.0	9.8	3.9	7.9
Corticalinised animal	15.0	7.6	11.9	11.6	13.6	12.7

Especially marked is the corticaline influence on the phosphagen concentration in the kidney where it is tripled and in the skeletal muscles where it is increased 3.5 times.

As in regard to glycogen the corticaline influence is especially marked under conditions of an increased demand for it — namely under conditions of increased destruction *i. e.* in adrenalectomised animals and during muscle work.

After adrenalectomy most of the organs lose their storage of creatinine phosphate. The phosphagen phosphorus content in the skeletal muscles is decreased from 3.9 to 3.2 mg per cent, in the kidney from 4.0 to 1.0 mg per cent and in the brain from 7.9 to

4.3 mg per cent. But when corticaline is administered to adrenalectomised animals the phosphagen content in the above mentioned tissues is increased not only to normal, but even exceeds it. Thus in the skeletal muscles of an adrenalectomised and at the same time corticulinised animal the phosphagen phosphorus concentration is on the average 6.6, in the brain 13.3, in the kidney 22.8 mg per cent. Thus corticaline restores the capacity of synthesising creatine phosphate disturbed by adrenalectomy.

This increase in the creatine phosphate synthesis under corticaline influence is especially marked in a normal animal during muscle work which is followed by a loss of phosphagen. Data on the influence of corticaline on the creatine phosphate resynthesis during and following muscle exercises are given in the following table.

Creatine phosphate phosphorus content (in mg per cent).

	Muscle	Liver	Brain
<i>Control animals</i>			
Rest	23	27	29
Fatigue	18	12	37
Repose	24	17	79
<i>Corticulinised animals</i>			
Fatigue	32	30	50
Repose	84	42	85

As may be seen from the given table there is a loss of phosphagen storage in the muscle during muscle exercise. Its content is decreased. But during an hour of repose the phosphagen content regains its normal level — the resting level. When, however, corticaline is administered before muscle work the phosphagen resynthesis is performed so quickly that the loss of it may not be recognized. Immediately after work the phosphagen content in the muscle of a corticulinised animal is higher not only in a fatigued control animal but even higher than in a control animal under resting conditions. This increased synthesis is continued also during repose so that the phosphagen content in the muscle of a corticulinised animal is 3.5 times higher than in a control animal under resting conditions.

In the liver of a normal mouse the phosphagen loss during muscle work is higher than in the muscle. During muscle work the liver loses more than half of its storage. The storage is gradu-

ally restored during repose. But this restoration is performed so slowly that in an hour after work there is still little phosphagen in the liver, much less than in the liver of a resting animal. But when corticaline is administered to the animal before muscle work the synthesis of the used up phosphagen takes place so rapidly that at the height of fatigue there is much more phosphagen in the liver of a corticalinised animal not only in comparison with the liver of a fatigued control animal, but even more than in the liver of a resting control animal. This increased synthesis continues also during repose following work. But while in the liver of a control animal this reparation does not reach the rest level, in the liver of a corticalinised animal it is 1.5 times higher than the rest level.

In the brain the phosphagen synthesis is also increased by corticaline. The phosphagen content in the brain of a corticalinised animal in a state of fatigue and after repose is higher than in the brain of fatigued and reposed control animals.

Hexose Phosphate.

An analogous influence is synthesis of another ether of phosphoric acid which plays a very important rôle in carbohydrate metabolism and during muscle work — namely on the synthesis of sugar ethers of phosphoric acid. As in the synthesis of glycogen and phosphagen corticaline favours the etherisation of the sugar by phosphoric acid and especially it favours this etherisation during adrenal insufficiency and during muscle work *i. e.* under conditions of limited possibilities and increased demand.

Concentration of hexose phosphate (in mg per cent).

	Intestinal wall	Heart	Muscle
Normal animals	793	1123	718
Adrenalectomised animals	522	591	303
Corticalinised animals	1089	2035	1079

It may be seen from the above average data that the hexose phosphate content in the heart, intestinal wall and skeletal muscles of an adrenalectomised rabbit is less than in the organs of a normal one. Especially the skeletal muscles suffer in this regard; their hexose phosphate content is decreased more than

twice. After corticoline administration to the adrenalectomised animals the hexose phosphate content not only reaches the normal, but even considerably surpasses it. In the intestine it is doubled, in the heart it is 2.5 times more, in the skeletal muscles it is three times more. Corticoline thus compensates the insufficient synthesis of hexose phosphate caused by adrenalectomy.

As in regard to glycogen and phosphagen corticoline favours the resynthesis of hexose phosphate during muscle work. It is increased not only in the muscles but also in the liver and in the brain as may be seen from the given table.

The hexose phosphate content in tissues of a mouse (in mg per cent).

	Muscle	Liver	Brain
Rest	325	310	527
Fatigue	131	109	228
Corticalinisation	688	477	801

Liver, brain and skeletal muscles lose more than half of their hexose phosphate storage during work. But if corticoline is administered to the animal before work the hexose phosphate content in all organs taken from a fatigued animal is considerably higher than in the organs of a fatigued control animal. In the brain it is 3.2 times more, in the liver 4 times more, in the skeletal muscles almost 5.5 times more. The hexose phosphate content in the organs of corticalinised animals taken immediately after muscle exercise is higher than its content in the organs of a resting control animal. This allows us to assume that the resynthesis of hexose phosphate during muscle work under corticoline influence exceeds the decomposition and the loss of this energetic material.

Summary.

The physiological importance of corticoline probably lies in ensuring the synthetic phase of carbohydrate metabolism. Its active rôle in carbohydrate metabolism is in distinct contrast to its almost total indifference to protein metabolism. The protein and nitrous content of the organs undergoes very little change after corticoline administration, just as after adrenalectomy. The active rôle of corticoline in carbohydrate metabolism also contrasts with its indifference to water and salt metabolism. In this

respect corticaline differs from some steroid components of the adrenal cortex.

The capacity of corticaline to accelerate the reparative phase of carbohydrate metabolism during muscle work may be used for the prophylaxis of fatigue following intensive work.

It is possible that corticaline may be useful in the therapy of some cases of heart muscle weakness as a factor facilitating the storage of creatine phosphate and hexose phosphate in the heart muscle. Our results allow us to assume that the administration of glucose in the therapy of heart muscle weakness may become more effective if corticaline is administered simultaneously.

Thus corticaline is a hormone the rôle of which consists in facilitating the synthetic reparative phase of carbohydrate metabolism *i. e.* a hormone facilitating rest and which therefore deserves to be called »hormone of rest».

On February 16, 1946 we sent to Russia the proof-sheets of this paper but have not been able to get them back, notwithstanding a telegram and a number of letters. At the request of the Soviet Embassy in Stockholm we sent through the Embassy on November 19, 1947 a second copy of the proof-sheets. As we have not as yet received an answer or got the proof-sheets back, we have been obliged to publish the article without any possible corrections that the author might have wished to make.

The Editor.

From the Laboratory for General Pathology of the University
of Amsterdam.

On the Biological Activity of Iodinated Proteins and Thiourea.

By

Prof. Dr. P. FORMIJNE.

(Submitted for publication March 28, 1947.)

The study of the anti-thyroidal substances has its origin in the discovery of Chesney (1) that rabbits develop a goitre on a diet with special vegetables, for instance cabbage. By a long series of investigations this phenomenon was clarified and it was shown that several substances can inhibit the action of the thyroid gland. Astwood (2) gave for the first time inhibitory substances of this kind, especially thionrea and thiouracil, to human beings with hyperthyroidism. He found a marked inhibitory influence of these substances on the increased function of the thyroid. The mode of action of these substances has been studied by many authors. It was found that the action of the thyroid-hormon and of thyroxin was not modified by these substances and gradually the supposition that thiourea and the other related substances inhibit the formation of thyroxin in the living body was accepted. Rawson, Tammheimer & Peacock (3) showed by means of radioactive iodine that thiourea inhibited the fixation of iodine by the thyroid gland. Dempsey, De Robertis & Williams (6) studied the action of thiourea in normal animals. They also came to the conclusion that the synthesis of thyroxin is inhibited by thionrea. They held the view that the enzymatic system, which is responsible for the synthesis of thyroxin was disturbed by thiourea. This view has been accepted by many authors in the literature.

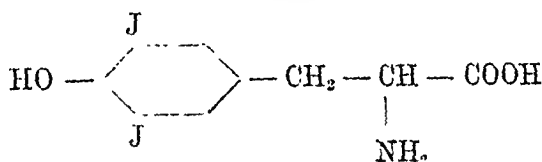
In a preceding communication it could be shown that thiourea can inhibit the formation of thyroxin in vitro beyond any action on enzymes. The supposition can therefore be made that the action of thiourea in the body also is a purely chemical process without intervention of enzymes.

The mutual interaction of iodine and thiourea has already been known for a long time in chemical literature. At first addition of iodine to thiourea was suspected. Later it was found, especially by Werner (7) that the reaction between iodine and thiourea is dependent on an equilibrium which is different with different concentrations. There is no true addition of iodine but there is formation of the hydro-iodide of formamidine disulphide:

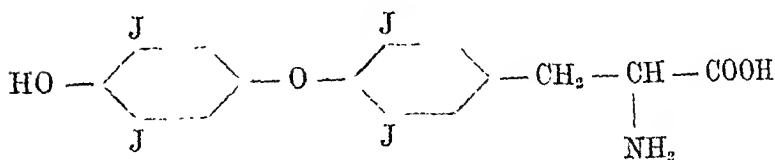


If iodine is added to protein a chemical addition takes place. The main part is bound by the tyrosine molecules with formation of diiodotyrosin which in pure form has no biological activity. However it was already found a long time ago that the iodinated product of many proteins can have a biological activity which resembles thyroxin.

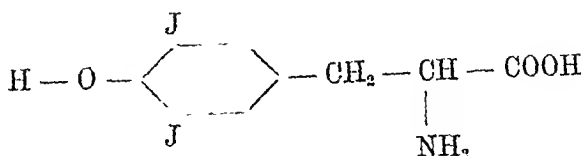
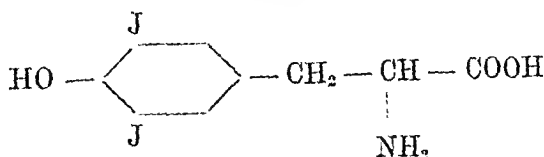
Ludwig & von Mutzenbecher (8) succeeded in isolating a small quantity of pure thyroxin from iodinated proteins, thereby proving that this iodination, which mainly gives diiodotyrosin, also results in the formation of some thyroxin by the oxydative coupling of two molecules of diiodotyrosin:



Diiodotyrosin



Thyroxin



In the afore mentioned investigation it was found that this formation of thyroxin during the iodination of protein can be inhibited by the previous addition of thiourea. For this purpose the products of the iodination were hydrolysed with barium-hydroxyde and the acid-insoluble fraction isolated and solved in normal NaOH. Leland & Foster showed that the separation between thyroxin and other iodine containing substances can be effected by extraction of the alkaline solution with butylalcohol in a specified manner.

This ingenious method was found to be very useful for the present investigation on contrast with the isolation of thyroxin in pure form which is tedious and does not give quantitative results. In a series of experiments of this kind a definite inhibition of thyroxin-formation by thiourea could be demonstrated.

The following experiment can be given as an example. After the iodination of 20 g of casein (sol. B) there was found after isolation an amount of 30 mg of thyroxin-iodine in the butylalcohol-extract. At the same time the iodination was carried out in exactly the same way with 20 g of casein. The only difference was that before the iodination 6 g of thiourea were added (sol. A). In the product there was found after hydrolysatation and isolation of the acid-insoluble fraction and extraction with butylalcohol only 3 mg of thyroxin-iodine.

This experiment showed that the formation of thyroxin was inhibited to a great extent by thiourea. It was desirable to check these results with a biological method for which the metamorphosis of tadpoles was chosen. This can be accelerated by very small amounts of thyroxin while other iodine-containing substances only act in quantities which are much higher than for thyroxin. Deanesley, Emmet & Parkes (9) studied this test recently and found it satisfactory. The biological experiments were carried out in the following way:

An aliquot quantity of the iodinated product that was formed without the presence of thiourea (sol. B) was compared with the product formed by the iodinating of a thiourea containing protein-solution (sol. A). The total amount of thyroxin-iodine in sol. B was, beginning with 20 g casein, 30 mg, while in solution A, starting from the same amount of casein, this time with 6 g of thiourea, only 30 mg of thyroxin-iodine was found.

The tadpoles were brought in beakers with 400 ml of ditchwater in groups of ten. They were 5 days old. The experiment was

started on April 26th. The mean total length as measured on the living animals in all beakers was 17 mM. In beaker I an amount of 4 mg thyroxin-iodine from solution B was added, thus $\frac{4}{3} \times \frac{1}{10}$ of the total amount (30 mg in solution B). In beaker III $\frac{1}{10}$ of this quantity was added, thus $\frac{4}{3} \times \frac{1}{100}$ of the total amount from sol. B, in beaker V $\frac{4}{3} \times \frac{1}{1,000}$.

In the same way in beaker II was placed 0.4 mg thyroxin-iodine from sol. A, being also $\frac{4}{3} \times \frac{1}{10}$ of the total quantity (3 mg in sol. A). Beaker IV contained $\frac{4}{3} \times \frac{1}{100}$ of the total amount from sol. A, beakers VI $\frac{4}{3} \times \frac{1}{1,000}$. Beaker VII was the control. The odd and even numbers were thus comparable because they contained an equal fraction of the original sol. B and A. It was found, that in all concentrations of solution A not the slightest difference was observable in connection with the control. In this solution no biological active substance could be demonstrated. The most important results of these experiments were collected in table I.

Table I.

First series.

T. L. = total length, B. L. = bodylength, B. B. = bodybreadth.

Exp.	Sol.	Total J.	T. L. $\frac{26}{4}$	B. L. $\frac{26}{4}$	T. L. $\frac{1}{5}$	B. L. $\frac{1}{5}$	B. B. $\frac{1}{5}$	T. L. $\frac{2}{5}$	B. L. $\frac{2}{5}$	B. B. $\frac{2}{5}$
I.....	B	4 mg	17	6	13.4	5.6	2.8	10.6	5	2.5
II.....	A	0.4 »	17	6	21.2	7.8	4.6	23.5	8.6	5.5
III....	B	0.4 »	17	6	17.4	6.2	3.4	18	6.1	3.4
IV....	A	0.04 »	17	6	21.3	7.8	4.6	23.7	8.5	5.3

These results show that under the influence of sol. B a rapid, progressive diminution of the total length takes place, and also a diminution of bodylength and bodybreadth. At the same time the typical change of bodyform took place. These changes were mostly marked in beaker I, containing 4 mg of thyroxin-iodine; in beaker III containing 0.4 mg thyroxin-iodine a distinct effect was also visible. Of great importance was the comparison of beaker II, containing the product from A, and beaker III, containing the product from B. In both an equal quantity of iodine was present (0.4 mg). Whilst in beaker III a distinct regression of the growth and a commencing metamorphosis, showing a biological active product, was found, in beaker II, with the same quantity of iodine, no effect on the metamorphosis was to be seen.

This was important in two ways.

In the first place it was shown that the effect on the metamorphosis, under the conditions of the experiment, was not dependent on the iodine content itself.

In the second place it was shown, that the small amount of iodine found by the method of Leland & Foster in sol. A (in this solution the iodinating process had taken place in the presence of thiourea) had no thyroxin activity. This experiment proved that the formation of a biologically active product during the iodination of protein was completely inhibited by thiourea.

In beaker I (with 4 mg of thyroxin-iodine from sol. B) a rapid metamorphosis appeared, but on May 3rd all tadpoles except one, were dead.

It is known, that in a relatively high concentration of thyroxin such a rapid metamorphosis takes place, that the transition from tadpole to frog is disturbed in such a way that life becomes impossible. The only surviving tadpole from beaker I lived till May 5th and had then already a left foreleg, while in all other beakers the forelegs were absent. On May 6th the size of the still living tadpoles was measured.

Table II.
First series.

Exp.	Sol.	Total J	T. L. mm	T. L. mm
II.....	A	0.4 mg	17 mm	30 mm
III.....	B	0.4 »	17 »	20 »
IV.....	A	0.04 »	17 »	30 »
V.....	B	0.04 »	17 »	28 »
VI.....	A	0.004 »	17 »	29 »
VII.....	control		17 »	30 »

This shows distinctly that in the even beakers (progressive dilutions from sol. A) no difference with the control could be seen.

In beaker III (sol. B first dilution) a distinct inhibition of growth was present, while in beaker V this was dubious. These experiments demonstrated that the iodination of protein *in vitro* leads to the formation of a biologically active fraction, but that the formation of this biologically active substance was inhibited completely by the presence of thiourea.

This result led to a re-investigation of the chemical part of the experiment as the slight amount of »thyroxin-iodine« in sol. A did not show biological activity. All chemical determinations had been checked carefully with blank experiments. But it was found

in going over the experiment again that the butyl-alcohol, used for the extraction, had not been considered in the blanc experiment.

In a new chemical experiment in which the whole determination was repeated and carefully checked with blanc experiments, including the butyl-alcohol, the following results were obtained:

In sol. B, obtained from 10 grams of casein iodinated with 20 ml of Lugol's solution, containing 1 g of iodine, after hydrolysis an isolation of the thyroxin-fraction, 30.6 mg of iodine could be found.

In sol. A, in which 10 g of casein was iodinated with the same amount of Lugol in the presence of 3 g thiourea after hydrolysis and isolation of the thyroxin-fraction no difference with the blanc determination was found.

Therefore no thyroxin was found present in this solution. The results obtained were thus:

Sol. B: 30.6 mg of thyroxin-iodine.

Sol. A: 0 mg of thyroxin-iodine.

In a control experiment the relation between the action of pure thyroxin and NaJ was investigated. In this experiment the effect of 3.6 mg of thyroxin-iodine was compared with 10 mg of iodine as NaJ.

Table III.
Second series.

Exp.	Additional substance	T. L. ‰/4	T. L. ‰/4
I.....	3.6 mg thyroxin J.	19	18
II.....	10 mg J. as NaJ	19	29
III.....	Control	19	30

The thyroxin-iodine led to a clearcut inhibition of the growth and to the development of a rapid metamorphosis. After 5 days all tadpoles in this beaker with one exception were dead. In some the development of left forelegs was present.

In the experiment with NaJ no inhibition of growth was seen in comparison with the control without addition of iodine. There was no sign of an increased metamorphosis in the beaker with NaJ. This experiment demonstrated that iodine as such had no influence on the metamorphosis even in a concentration which was much higher than in the first series of experiments. It could be concluded that the biological activity which was observed must be attributed to iodine incorporated in the thyroxin molecule.

In some further experiments the difference in the action of thyroxin, thyroxin + thiourea and thiourea only on growth and metamorphosis was investigated.

It was expected that thyroxin could lead to a rapid metamorphosis and inhibition of growth and that this effect would not be changed by the addition of thiourea. Furthermore it was expected that thiourea alone would cause an inhibition of metamorphosis.

The results of these experiments were partly at variance with our expectations. Thyroxin, in a concentration of 4 mg on 400 ml caused a severe inhibition of growth and a rapid metamorphosis (already after 5 days); the rate of metamorphosis and inhibition of growth was the same if 40 mg of thiourea were added to 4 mg of thyroxin.

This experiment showed that thiourea cannot modify the activity of already formed thyroxin. Thiourea alone in a concentration of 40 mg on 400 ml effected also an accelerated metamorphosis, compared with the control after a longer period; especially the development of forelegs was accelerated. Some differences with the changes caused by thyroxin could be seen. In the first place the tail remained long in the solution with thiourea during the development of the forelegs, as happens in normal metamorphosis, while the addition of thyroxin leads to shortening of the tail already in an early stage and later on to the formation of forelegs. It was further observed that with thyroxin the left foreleg develops first, while with thiourea the right foreleg develops first.

These experiments were repeated on May 18th with 1 mg of thyroxin, 1 mg thyroxin + 40 mg of thiourea and with thiourea only, in different concentrations, namely 40, 10, and 2½ mg.

Table IV.
Series IV.

Exp.	Additional substance	T.L. 18/5	T.L. 22/5	T.L. 23/5	Remarks
I	1 mg thyroxine....	35	22		2 with l. unformed foreleg 1 with l. foreleg and r. unformed foreleg
II	1 mg thyrox..... 40 mg thioureaum ..	35	22		1 with only hinderlegs all dead 2 with 2 forel. dead 1 with r. forel. dead
III	40 mg thioureaum ..	35	33	29	1 with l. unf. forel. dead 3 with r. foreleg 2 with only hinderl.
IV	10 mg thioureaum ..	35	33	32	no forelegs
V	2.5 mg thioureaum.	35	35	34	no forelegs
VI	control.....	35	37	36	no forelegs

After 4 days on May 22nd a distinct inhibition of growth had appeared in the beaker with thyroxin and in the one with thyroxin + thiourea. The total length had decreased from 35 mm to 22 mm. The control had grown to 37 mm. In the solution with thiourea (40 and 10 mg) the length was 33 mm, in that with $2\frac{1}{2}$ mg 35 mm.

Thiourea had therefore also caused a definite, although moderate inhibition of growth. On May 23rd five days after the beginning of the experiment three out of 4 tadpoles, in the beaker with thyroxin only, had a left foreleg or foreleg formation. In the beaker with thyroxin + thiourea two tadpoles had two forelegs, one only a left foreleg, one only a right foreleg. In the beaker with thiourea only (40 mg) three tadpoles had a right foreleg. In the beaker with 10 mg and $2\frac{1}{2}$ mg thiourea and the control no tadpoles with forelegs were found on this day.

These experiments demonstrated that thiourea in the dose of 40 mg on 400 ml water caused an acceleration of metamorphosis and not an inhibition. In the literature only a few publications on this subject were found.

Hughes & Astwood (13) showed that in tadpoles from *Rana clamitans* the metamorphosis induced by injections of thyrotropine could be inhibited with concentrations of thiouracil between 1/2,000 and 1/10,000. Bruce & Parkes (14) investigated the action of thiourea and thiouracil in *Discoglossus pictus*. They found a marked inhibition of metamorphosis in the tadpoles of this species. These investigations, although carried out with other species, were at variance with the results described above. For this reason it will be necessary to repeat and extend these experiments in the next season.

Summary.

The formation of thyroxin in vitro during the iodination of casein can be inhibited by the previous addition with thiourea. To demonstrate this the iodinated products were hydrolysed, the acid-insoluble fraction separated and the thyroxin fraction isolated with the butylalcohol method of Leland & Foster. The biological activity of the isolated products was tested by the action on the metamorphosis of tadpoles. Both the chemical and the biological method showed the inhibition of thyroxin-formation in the presence of thiourea. A mixture of thiourea and pure thyroxin showed the same biological activity as thyroxin alone.

Thiourea alone in a concentration of 1:10,000 showed an acceleration of metamorphosis which result was at variance with the expectations and with previous publications.

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Addendum.

After completion of this article, it was found by personal communication from Astwood, that the view, expressed in this article is similar to one of the hypotheses which Astwood has suggested for the action of the thio-compounds.

Miller, Roblin and Astwood (J. Am. Chem. Soc.: 67: 2201: 1945) have shown that the uptake of iodine by caseine is inhibited to a large extent by the previous addition of thio-uracil. The inhibition of the formation of thyroxin has not been demonstrated by these authors, although this can be deduced from these experiments.

It is peculiar that this investigation is not cited in most of the recent publications and is not generally known, so that the view about the action of the thio-compounds on an enzymatic process is still widely prevalent.

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Chief: Tr. Schønfelder.

Incidence and Correlation with Clinical Severity of *Typus gravis*, *mitis*, and *intermedius* of *Corynebacterium diphtheriae* in Bergen and Surrounding Areas.

By

TH. M. VOGELSANG and ALF ØDEGAARD.

(Submitted for publication May 12, 1947.)

In Leeds, Anderson, Happold, McLeod and Thomson (1931) found on investigating a series of strains of *Corynebacterium diphtheriae* that there was a remarkable relationship between the clinical picture and the cultural and biochemical properties of these strains. They described two quite distinct types — *Bacillus diphtheriae gravis* and *Bacillus diphtheriae mitis*. *Typus gravis* was apt to give rise to toxic and malignant diphtheria and also to be responsible for epidemics, whereas *typus mitis* was found in light and sporadic cases, but was apt to extend down to the larynx and to give rise to serious obstructive phenomena and pneumonic complications.

In addition to these two distinct types, Anderson, *et al.* also found a few intermediate forms with constant characters. These forms have subsequently been investigated more closely by Anderson, Cooper, Happold and McLeod (1933) and by Mair (1936). A third type — *typus intermedius* — has been described; like *typus gravis* it may give rise to severe toxic cases of diphtheria, but it is less liable than this type to give rise to epidemics.

More recently a series of investigations has been undertaken in various parts of the world into the occurrence of these types

whose classification has, on the whole, been confirmed. There are, however, several observers who are not in agreement over the toxicity of the various types. For example, Parish, Whatley and O'Brien (1932) found that *typus mitis* could be just as malignant as *typus gravis* and could produce greater quantities of toxin than it did. Menton (1932) maintained that there was no biological foundation for the terms *mitis* and *gravis*. Robinson and Marshall (1934) found that in Manchester *typus intermedius* gave rise to at any rate just as many and as fatal cases as *typus gravis*. Both from English quarters, Ewing (1933), Wright and Christison (1935), and from German quarters, Hammerschmidt (1937), the suggestion has come that the types should be given a more neutral nomenclature in the form of letters or numbers.

Although in a few local epidemics *typus mitis* can give rise to toxic diphtheria, and numerous light cases of diphtheria may be due to *typus gravis*, yet the opinion of Anderson, *et al.* of the toxicity of the various types has been confirmed by large statistics. McLeod (1943) has summarized observations on the correlation of clinical severity and types of *Corynebacterium diphtheriae* recorded in Australia, Scotland, England, Germany, Poland, South Africa, Russia, the U. S. A. and Holland. This series gives a grand total of about 25,000 cases. *Typus gravis*, with an 8.1 per cent. mortality was found in 11,492 cases, *typus mitis*, with a 2.6 per cent. mortality was found in 6,858 cases, and *typus intermedius*, with a 7.2 per cent. mortality, in 6,807 cases. According to this comprehensive analysis the *typus intermedius* mortality was almost as high as that of *typus gravis* and three times as high as that of *typus mitis*.

There are, however, diphtheria strains which in one or more directions differ from the above three types and are therefore to be described as atypical. Such atypical strains were found in 663 cases in McLeod's statistics. There were 24 deaths (3.6 per cent.) among these cases.

The frequency with which such atypical strains occur, varies from place to place, and is greatest in the localities where diphtheria tends to be sporadic and runs a mild or moderately severe course. These strains are usually found in carriers and convalescents, but now and then they have been observed in severe and fatal cases of diphtheria. Epidemics of diphtheria caused by such atypical strains have not been observed.

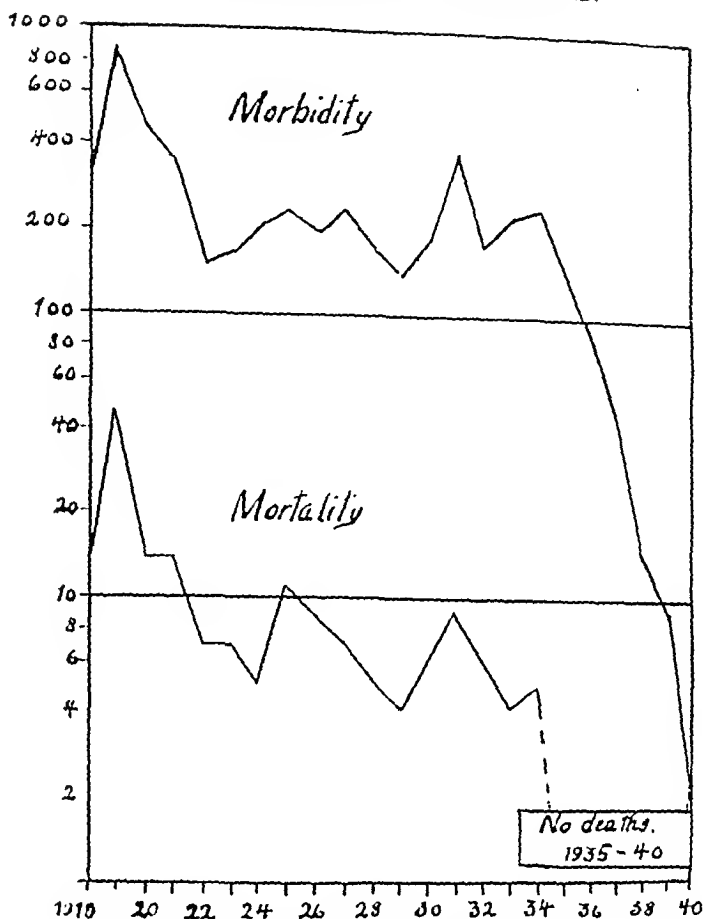


Fig. 1. The Diphtheria morbidity and mortality pr. 100,000 inhabitants in Bergen 1918—1940.

The Occurrence of Diphtheria in Western Norway between the Two World Wars.

As Fig. 1 shows, there was a slow and even decline in the occurrence of diphtheria in Bergen between the two world wars.

In 1919 there were 8.73 notifications per 1,000 inhabitants. In 1931 this figure was reduced to 3.71, in 1935 it was down to 1.45, and it fell still further during the following years, reaching its lowest level in 1940 with 0.02 notifications per 1,000 inhabitants.

Whereas the mortality from diphtheria per 1,000 inhabitants in Bergen in 1919 was 0.46, it was down to 0.09 in 1931, and in the period 1935—1940 there was not a single death from diphtheria in Bergen.

In the districts adjoining Bergen and in the rest of Western Norway there were also only some local epidemics and altogether a few cases between the two world wars.

In 1936—1937, K. Schnitler undertook type determinations of the strains of diphtheria isolated at Gade's Institute from specimens sent to it from Bergen and Western Norway.

For some years isolated cases and small epidemics of diphtheria were observed from time to time at a coastal hospital near Bergen. From 1932 onwards its occupants were therefore immunized by Ramon's toxoid. In 1937 a light case of diphtheria was observed in a recently admitted patient who had not yet been thus immunized. As a sequel to this case, several light cases were observed among the other patients previously immunized. At the investigation undertaken on this occasion, 19 strains of diphtheria bacilli were isolated. Among the patients with clinical manifestations of the disease there were 7 in whom *typus intermedius* was found and 1 in whom *typus mitis* was found. Among the other patients who were regarded as carriers there was one in whom *typus intermedius* was found. The others harboured *typus mitis*.

Schnitler's material consisted of altogether 93 diphtheria strains. Apart from the 8 *typus intermedius* strains from the mild epidemic at a coastal hospital just referred to, all the remaining 85 strains belonged to *typus mitis*. *Typus gravis* was not once found in Western Norway during the 2 years with which Schnitler's investigations were concerned.

The Present Diphtheria Epidemic in Bergen.

After a quiet period of 6—7 years, the present diphtheria epidemic in Bergen began at the end of 1941 and grew in 1942 and 1943. Fig. 2 and table 1 give the morbidity and mortality. The

Table 1.
Diphtheria Morbidity and Mortality in Bergen 1941—1946.

Year	Nr. of cases	Deaths	
		Nr.	%
1941	18	0	—
1942	266	10	3.8
1943	519	9	1.7
1944	501	28	5.6
1945	185	12	6.5
1946	147	10	6.8

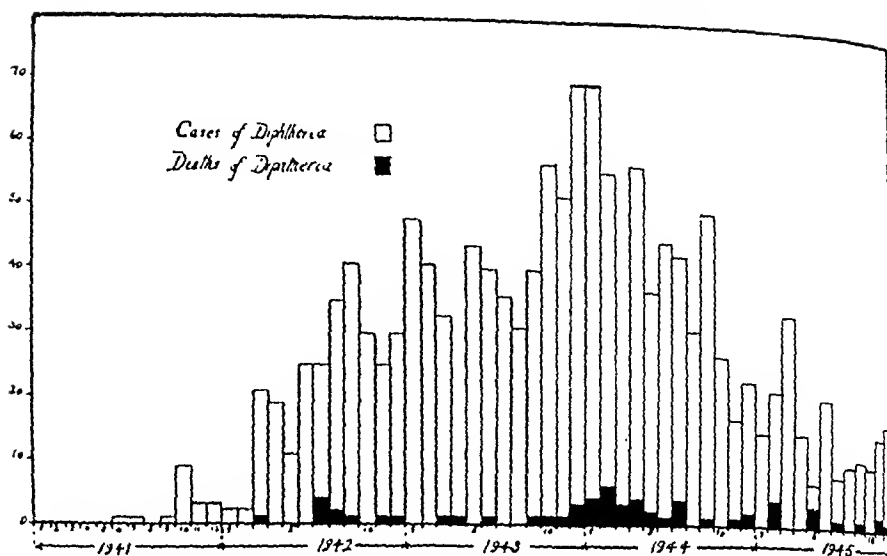


Fig. 2. Cases of Diphtheria and deaths from it in Bergen 1941—1945, in each month of the year.

epidemic culminated in the winter of 1943—1944, since when it has shown a tendency to decline slowly. With its culmination, the epidemic seemed to have acquired a more severe character with a higher mortality. During the first three years of the epidemic, 1941—1943, the average mortality was 2.4 per cent., whereas during the three last years, 1944—1946, it rose to 6 per cent.

In the autumn of 1942, compulsory diphtheria immunization was carried out on the children in the elementary schools in Bergen, two injections of diphtheria toxoid being given four weeks apart. In the autumn of 1943 each child received a third injection and practically every school child was thus immunized.

In the spring of 1944, a search was made (Vogelsang and Knutsen) for diphtheria bacilli in the throats and noses of 3,307 actively immunized children in the elementary schools of seven different school districts in Bergen. Sixty (1.8 per cent.) were found to be carriers. Type determinations of the isolated strains showed 31 of them to belong to *typus intermedius*, 20 to *typus mitis*, 8 to *typus gravis* and 1 to be atypical. This atypical strain and one of the *typus mitis* strains were avirulent. It will thus be seen that *typus intermedius* was the predominant type in this material (52 per cent.) whereas *typus mitis* and *typus gravis* constituted 33 and 13 per cent. respectively.

Diphtheria Typing in 1944-1945.

In order to ascertain the distribution of the different types among the patients in this epidemic and the relationship of type to clinical picture, an attempt was made between March 1944 and April 1945 to obtain pure cultures of, and to type-determine, as many diphtheria strains as possible from the patients suffering from diphtheria in the Department for Infectious Diseases of the Bergen City Hospital. Its diphtheria patients come primarily from the town itself. In the neighbouring districts there are no permanent fever hospitals. During this epidemic a provisional hospital had to be equipped, but in so far as space allowed, diphtheria patients from districts adjoining the town were also admitted to the City Hospital. Some of these cases were very severe or they were cases of croup requiring hospital treatment. It follows that the proportion of severe cases was higher in this hospital than outside it.

It would have been desirable, but it was for various reasons impossible, to type-determine all the cases of diphtheria treated in this hospital in the period under review.

Technique.

The technique adopted in these investigations was the same as that employed by Vogelsang and Knutsen (1944) in the already mentioned examinations of diphtheria strains isolated from immunized school children in Bergen.

Material from macroscopically and microscopically pure cultures was added to the following varieties of sugar, galactose, glucose, saccharose and glycogen. Only those strains which formed acid in the two first of these sugars, but not in saccharose, were regarded as diphtheria bacilli.

The colonies on McLeod's medium were examined with the aid of a binocular plate microscope. The capacity of a strain to haemolyse erythrocytes was examined on blood plates according to Tarnowski's (1942) 2-layer method, with a thicker layer of ordinary nutrient broth agar at the bottom of a Petri dish, and over this a thin layer of blood agar. Sheep's blood (5 per cent.) was employed. The appearance of the colonies and their capacity to haemolyse were compared with their growth in nutrient broth

and their capacity to ferment glycogen. In table 2 are presented some of the most important distinctive features of the diphtheria types.

Table 2.

Some of the Most Important Distinctive Features of the Diphtheria Types.

Type	Mitis	Intermedius	Gravis
Morphology	Long forms with metachromatic granules.	Barred forms often clubbed at ends.	Short forms usually no granules.
Appearance of growth on McLeod's medium.	Smooth, convex, shining colonies with black centre and greyish periphery. Regular margin.	Small, dark colonies very uniform in size. Small central papilla. Slightly raised margin.	Large, dull, greyish to black colonies with radial striations. Irregular margin.
Hemolysis 5 % sheep's blood agar	+	0	+ or 0
Appearance of growth in nutrient broth	Diffuse turbidity	Finely granular turbidity	Clear fluid with pellicle and granular sediment
Fermentation of glycogen	0	0	+

Own Investigations.

Altogether 232 diphtheria patients were examined without any process of selection, every patient admitted in the periods within the time limit referred to being included in this study.

Table 3.

The Cases of Diphtheria According to the Age of the Patients.

Age	0—5 years	6—15 years	Over 15 years
Nr. of cases ...	56	26	150
♂	29	13	45
♀	27	13	105

Table 3 gives the age distribution of the patients. As compared with usual findings elsewhere, there were remarkably few patients of school age in our material. This may be so because active im-

munization of the children in the elementary schools in Bergen was carried out in 1942—1943 and was also extended to the neighbouring areas. While, for example, in an epidemic of diphtheria in Bergen in 1910, more than half the patients were of the school age, only 3 per cent. of them were between the ages of 7 and 14 in 1944, and only 4 per cent. in 1945.

While there were as many boys as girls, there were more than twice as many women as men in our material; this sex ratio is commonly to be found in other diphtheria statistics also.

Table 4.

Distribution of the Types According to the Age and Sex of the Patients.

Age	Sex	Mitis	Inter- medius	Gravis	Atypical
0—5 years	♂	8	11	10	—
	♀	11	11	5	—
6—15 years	♂	4	1	8	—
	♀	3	4	6	—
Over 15 years	♂	19	15	10	1
	♀	24	48	33	—
		69	90	72	1

Table 4 gives the distribution of the types according to the age and sex of the patients. It will be noted that *typus intermedius* was the dominating type, having been isolated in about 40 per cent., whereas *typus mitis* and *typus gravis* accounted for 30 per cent. each. A single atypical strain, responsible for a light case of diphtheria, was also found.

Typus mitis was about equally frequent in boys and girls, but more frequent in men than in women when due account is taken of the numerical predominance of the latter. *Typus intermedius* and *typus gravis* were also more or less evenly distributed among boys and girls, but were more frequent among women than men. Whereas women were about twice as numerous as men, *typus intermedius* and *typus gravis* were more than three times more frequent among women than men. The element of chance with such small figures as ours robs them, however, of much of their value. But, on the other hand, it is well to recall that these investigations were undertaken in wartime during which women in

particular were under a heavy strain, undernourished because they often satisfied their children's appetites at the cost of their own meagre rations. It is therefore conceivable that at this time women were more predisposed than men to infection with virulent diphtheria bacilli.

Table 5.
Relationship of the Types to the Clinical Picture.

Clinical picture	Mitis	Inter- medius	Gravis	Atypical	Total
Diphtheria of the throat					
Light cases	34	56	30	1	121
Severe cases	12	21	30	—	63
Diphtheria of larynx	16	4	7	—	27
Diphtheria of nose	1	5	1	—	7
Diphtheria of umbilicus	2	1	—	—	3
Diphtheria of ear	—	—	1	—	1
Diphtheria carriers	4	3	3	—	10
	69	90	72	1	232

Table 5 correlates the types with the clinical manifestations of diphtheria. At the Department for Infectious Diseases, diphtheria of the throat is classified thus:

- Grade I: Rubor and unilateral, insignificant diphtheritic membrane of a tonsil.
- Grade II: Bilateral false membranes not extending beyond the tonsils.
- Grade III: More widespread false membranes which extend over the tonsils and palatine arches. Slight oedema,
- Grade IV: Toxic diphtheria with severe diphtheritic membranes and oedema.

To avoid many grades with small figures, Grades I and II have been fused together in table 5 and are described as light cases, while Grades III and IV are classed as severe cases.

Among the light cases a strikingly large number of *typus intermedius* strains were found, nearly half of these cases being accounted for by this type. More than 60 per cent. of the *typus intermedius* strains had given rise to only light cases of diphtheria of the throat, and about one-fourth of the cases due to this type were more severe cases.

Half the *typus mitis* strains were associated with light cases and less than one-fifth with more severe cases of diphtheria of

the throat. *Typus gravis* was almost as frequent in association with light cases as was *typus mitis*, but in more severe cases the former was found more than twice as frequently as the latter. Nearly half the cases of more severe disease were traced to *typus gravis*.

There were remarkably many cases of croup in our material. Only four of them were, however, cases of pure larynx diphtheria, the overwhelming majority, 23 cases, being associated with diphtheria of the throat and bronchi. Here, as in other studies, *typus mitis* was the dominant type in diphtheria of the larynx, while *typus gravis* was found in about one-quarter of the cases.

The other groups are put on record to make this report complete, but they are too small to be a guide to the frequency with which these types occur.

Table 6.

Distribution of the Types According to Their Incidence every Quarter of the Year under Review.

Type	First quarter	Second quarter	Third quarter	Fourth quarter
Mitis	15 (32 %)	22 (27 %)	17 (27 %)	15 (37 %)
Intermedius	21 (46 %)	33 (41 %)	25 (40 %)	11 (26 %)
Gravis	10 (22 %)	26 (32 %)	21 (33 %)	15 (37 %)

During the day-by-day work at the Department for Infectious Diseases while these investigations were proceeding, we gained the impression from the clinical material that at first the admissions represented mainly light cases, and that the disease gradually acquired a more serious character. We have therefore indicated in table 6 the distribution of the different types in the quarters of the year — from March 1944 to April 1945 — during which these investigations were carried out. This table shows that while *typus mitis* was distributed more or less evenly over the four quarters, *typus intermedius* became gradually more rare, its place being taken by *typus gravis*. By thus splitting up our material, our figures have become quite small, but our clinical impression of the growing seriousness of the disease tallies with the apparent increase in the number of *typus gravis* cases.

Table 7 gives the neurological complications in relation to the different types. While *typus mitis* and *typus intermedius* were seldom associated with pareses, we see that about one-fifth of the

patients infected with *typus gravis* developed neurological complications. Even this figure is small, but this is so because they refer only to the patients developing neurological complications in hospital and to those about whom we received reports after their discharge. For want of hospital beds the patients had to be discharged as early as possible and it is therefore probable that on returning home several patients developed pareses not always reported to us.

Table 7.

Relationship of the Types to Neurological Complications.

Type	Mitis	Inter- medius	Gravis	Total
Nr. of cases.....	4	8	13	25
Per cent.	6 %	9 %	18 %	11 %

It would have been interesting also to investigate the relationship of the different types to other complications such as myocarditis. But during the period under review we were unable to undertake electrocardiographic examinations on any large scale. Among the 232 patients there were, however, six with clinical signs of myocarditis, two being infected with *typus mitis*, two with *typus intermedius*, and two with *typus gravis*.

Table 8.

Distribution of the Types According to the Mortality.

Type	Mitis	Inter- medius	Gravis	Total
Nr. of cases.....	6	1	4	11
Per cent.	8.7 %	1.1 %	5.6 %	4.7 %

Table 8 gives the mortality. Eleven of the 232 patients (4.7 per cent.) died. Fig. 2, giving the diphtheria mortality in Bergen in the same period, shows that in the last three quarters of 1944 there were 15 deaths among 330 cases of diphtheria, and in the first quarter of 1945, four deaths among 71 cases, a total of 19 deaths among 401 cases, *i. e.* a mortality again of 4.7 per cent. for the whole of Bergen at this time.

There were four deaths among the 72 patients infected with *typus gravis* and only one death among the 90 patients infected with *typus intermedius*. Contrast this low mortality with the six

deaths among the 69 patients (8.7 per cent.) infected with *typus mitis*. In most other statistics the *typus gravis* and *typus intermedius* infections show a considerably higher mortality than the *typus mitis* infections, whereas the reverse is to be noted in our material. In McLeod's big statistics, the mortality for *typus mitis* infections was 2.6 per cent. Our own high mortality is due to the fact that all the six patients who died suffered from diphtheria of the larynx with pulmonary complications. In the absence of obstruction of the respiratory tract, none of our *typus mitis* infections terminated fatally.

Among the patients developing diphtheria at the school age there were four who had previously undergone active immunization by diphtheria toxoid. But though *typus gravis* was found in these cases, the disease ran a mild course. The following shows how immunization may increase resistance: In a family with four children, the three youngest — two uni-ovular twin brothers aged 5 and a girl aged 6 — developed severe toxic diphtheria of which one of the twins died. The fourth child, a girl of 9 who had been immunized against diphtheria at school, developed a diphtheritic tonsillitis. She made a rapid recovery. *Typus gravis* was found in all four cases.

Discussion.

We have succeeded with 232 diphtheria strains obtained from clinical material in grouping them in the three types *gravis*, *intermedius* and *mitis* according to the appearance of the colonies on McLeod's medium, the haemolytic capacity of the different strains and their fermentation reactions. Although some experience is required of such an examination, it is not as a rule very difficult to distinguish the three types from each other. But we must bear in mind that there may be certain variations in the colonies of one and the same type. In this respect the degree of moisture, for example, of the culture medium plays a certain part. In our type determinations we have paid special attention to the fact that *typus gravis* ferments glycogen, *typus mitis* shows smooth haemolytic colonies, and *typus intermedius* grows as small, non-haemolytic colonies. The atypical strain yielded haemolytic colonies with the appearance of that of *typus gravis*, but it did not ferment glycogen.

Murray (1935) has shown that, by absorption of agglutinins, it is possible to distinguish the three types serologically also, but

that within each type there are several sub-groups serologically distinguishable. Tarnowski (1942) who has undertaken a searching investigation of the serological characteristics of diphtheria bacilli, has suggested that the three types should be called groups, the term »type» being reserved for serologically distinguishable sub-groups. The older use of the term »type» is, however, still preferred by most investigators for the classification of various strains according to their cultural and biochemical properties.

In the 1930ties in Central Europe there was a rise not only in the number of cases of diphtheria but also at the same time, and to a marked degree, in the toxicity of the disease. In Berlin, this change in the behaviour of the disease began as early as 1927. The mortality among diphtheria patients admitted to the Virchow Hospital in Berlin in 1924 was 5 per cent., and in the first 5 months of 1927 it had rocketed up to 26.7 per cent. (Deicher and Agulnik 1927). Type determinations of strains of diphtheria bacilli in Berlin by Schiff and Werber (1935) showed that *typus gravis* constituted 78 per cent., *typus intermedius* 12.3 per cent., and *typus mitis* 8 per cent. Gundel and Liebetruth (1936) who type-determined a series of strains from different parts of Germany, showed that throughout this country there was a very marked predominance of *typus gravis*.

This predominance seems to have persisted in Germany. At the beginning of the last World War, Herrmann's (1941) epidemiological studies showed a difference in the pathogenic properties of the different types, *typus gravis* being predominant in diphtheria patients, while *typus mitis* was the most common find in healthy carriers. The disease seems, however, gradually to have become less malignant. Thus in Frankfurt a. d. Oder, Grossmann (1942) found a diphtheria mortality of 9 per cent., three-quarters of his cases being due to *typus gravis*.

The present diphtheria epidemic, which has extended over the whole of Norway, has been much less serious than it was in Central Europe in the 1930ties to judge by the Bergen figures. In our cases of diphtheria of the throat, about two-thirds were light and one-third severe. Among the latter there were, however, several which in spite of their markedly toxic character usually responded to antitoxin by recovery. There were altogether 11 deaths among the 232 patients who included 10 without any false membrane and who were regarded as carriers. After discarding the latter, the mortality was about 5 per cent. There

were four deaths among the 72 patients with *typus gravis*, only one death among the 90 with *typus intermedius*, and six among the 69 with *typus mitis*. All these six patients suffered from pulmonary complications and underwent tracheotomy.

In 1936—1937, the behaviour of diphtheria in Western Norway was on the whole mild. There were isolated cases and a couple of small local epidemics. During these years Schnitler (1938) found *typus mitis* predominant. *Typus intermedius* was found in a single, small, local epidemic. *Typus gravis* was found nowhere. There have been similar findings in many other places. For example, diphtheria strains from several places were sent to Robinson and Peeney (1936), but although they examined numerous strains from several different areas in Scotland, New York City, Copenhagen and India, they found no *gravis* strains from these areas.

The present diphtheria epidemic in Bergen began very mildly. The mortality was 2.4 per cent. in 1941—1943, but it has risen subsequently. Examining diphtheria carriers among actively immunized school children in Bergen during this epidemic, Vogel-sang and Knutsen (1944) found *typus intermedius* predominating. In the present material also we found *typus intermedius* oftener than the other types. However, during the year in which these investigations were carried out, it would seem that *typus gravis* has gradually become more frequent, displacing *typus intermedius*. Such a change in the behaviour of the types during an epidemic has been quite often noted and can be marked. Wright (1941) has investigated fully 8,000 cases of diphtheria in Liverpool in the period 1937—1940, and whilst in 1937 *typus gravis* was found in 34 per cent., in 1940, 70 per cent. were *typus gravis* cases. There was, however, only a slight rise in the mortality which was 5.69 per cent. in 1937 and 6.45 per cent. in 1940.

It is conceivable that this increase in the number of *typus gravis* cases during an epidemic is determined by a rise in the antitoxin level of the community resulting in the most virulent strains being primarily those which keep on spreading. This could, however, hardly have been the case in Bergen. After the epidemic had lasted three years, Vogelsang and Kryvi (1945) applied the Schiek test to 3,000 persons in Bergen who had not been immunized against diphtheria and whose ages ranged from 16 upwards. It was found that 67 per cent. were Schiek-positive — a remarkably high figure so far on in the epidemic in comparison with findings elsewhere. But in spite of this high proportion of

Schick-positive persons, the epidemic seems to be on the wane. It will therefore be interesting to continue these investigations during the further decline of the epidemic.

Summary.

During an investigation of the diphtheria types in 232 cases from Bergen and neighbouring districts in the course of an epidemic of diphtheria, *typus gravis* was found in 72 cases, *typus intermedius* in 90, and *typus mitis* in 69. In a mild case of diphtheria an atypical diphtheria strain was found.

While there were about twice as many adult women as men, *typus intermedius* and *typus gravis* were found more than three times as often in women as in men.

Typus gravis was found as often as *typus mitis* in mild cases of diphtheria of the throat, but in severe cases the former was more than twice as common as the latter. Among the *typus gravis* cases were 13 with neurological complications.

More than 60 per cent. of the *typus intermedius* strains gave rise to mild diphtheria of the throat only. Altogether there were 2 cases of croup, among which there were 4 cases of pure laryngeal diphtheria. Here *typus mitis* predominated. Of the 11 patient who died, four were infected with *typus gravis*, one with *typus intermedius*, and six with *typus mitis*, all the latter being case of croup with pulmonary complications.

It would seem that during the year in which these investigations were carried out, *typus gravis* became gradually more frequent, displacing *typus intermedius*.

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From the State Bacteriologic Laboratory, Stockholm.

Investigations into Acute Infections of the Respiratory Tract.

V. An Epidemic of Influenza B in the Winter of 1946¹

By

GUNNAR LÖFSTRÖM.

(Submitted for publication June 28, 1947.)

During the years that virus research on influenza has been in progress in Sweden the following observations have been made with regard to the etiology of the influenza epidemics that have occurred. In connection with an epidemic in 1943 a couple of cases of influenza B were diagnosed. In 1944 influenza A dominated, and I have already described in an earlier publication (3) a virus A epidemic at a military camp. The morbidity for diseases of the influenza type during 1945 was low in Sweden. Neither A nor B infections seem to have occurred (4). The investigations described in the present paper refer to the influenza of 1946.

Influenza occurred in various parts of the world during the infection season extending from the autumn of 1945 to the spring of 1946. As a rule the epidemics were mild, possibly owing to the fact that influenza B was the commonest form.

The following information on the 1945—46 influenza season has been obtained from the »Epidemiological Information Bulletin» published by UNRRA, as well as from various other sources.

During the autumn of 1945 fairly mild influenza epidemics occurred, mainly concentrated to the southern portion of the Western Hemisphere, particularly South and Central America,

¹ The expenses of this investigation were defrayed in part by a grant from Aktiebolaget Astra, Södertälje, Sweden.

and in October an epidemic was also experienced in the southern states of the U. S. A. Burnet and co-workers (1) described a widespread, though clinically mild, epidemic of influenza B that also occurred in Australia in the month of October. In the southern states of the U. S. A. the incidence of influenza showed a further increase in November and December, and in the western states also an increase was noted at the end of November. In general the cases were mild, from the clinical standpoint, and in the vast majority of cases, B virus proved to be the infecting agent.

In Europe, a fairly mild form of influenza epidemic occurred in Belgium. This was already over by the beginning of January. Both A and B viruses were isolated. In England (2), influenza B occurred in January, and Denmark also had a mild epidemic of influenza early in the month of January. We now come to the start of the Swedish epidemic.

Material.

From the newspapers, and from reports sent in by the military medical authorities, it became obvious in the middle of January, 1946, that an epidemic of influenza was spreading over the south of Sweden, being especially extensive in the towns of Karlskrona and Kristianstad. Samples of blood for the diagnosing of influenza were requisitioned from the military camps, and at the same time a request was published in Svenska Läkartidningen (6) that samples of blood should be sent in to the State Bacteriologic Laboratory in the case of patients suspected of having influenza. Two samples were requested, the one taken during the acute face of the disease and the other ten to fourteen days later, during the convalescent stage.

By the end of January the influenza had spread to the West Coast also. An attempt was then made to isolate virus from the epidemic which was in progress by direct inoculation into two ferrets which had been transported to the military camp at Uddevalla, the district then affected by the influenza. The animals were inoculated with the pooled throat washings from six of the men who had contracted acute clinical influenza the same day or the day before. This was, however, the only opportunity presented during this epidemic for attempting to isolate virus from acute cases.

During the months that followed, samples of blood were sent in from various parts of the country and were tested by the complement fixation test for the presence of antibodies against influenza virus A and B. In some instances, only one sample was obtained from each patient. Some of the samples which had been taken during the convalescent stage had such a high antibody titer, however, that this one sample was quite sufficient for diagnosis. When only one sample had been sent in from the acute phase of the disease, it was generally of

no value for diagnostic purposes. A serologic diagnosis was made in 205 cases, 350 serum samples being examined.

Methods.

Isolation of virus. Inoculation experiments were made according to a previously described method (3) with some modifications. The two initial ferrets were inoculated within fifteen minutes after taking the throat washings.

Further passages were done as described before, using suspensions of the nasal mucous membrane from the inoculated animals, which were killed on the fourth day after inoculation. Fifteen passages were done, two ferrets being used for each passage.

A suspension of nasal mucous membrane from each passage was also inoculated into six 13-day chick embryos. Before inoculation an amount of 1,000 Oxford units of penicillin per ml. was added to each suspension. During the inoculation the eggs were transilluminated and the injection of 0.05 ml was made from the base of the egg and through the air sac. The embryo was held on the point of the needle while the inoculation was in progress, so that the suspension would reach the amniotic sac. The eggs were kept for 48 hours at a temperature of 35° C and the chorioallantoic and amniotic fluids were then harvested under sterile conditions and were transferred to a fresh series of eggs. If hemagglutination of chick red blood cells was obtained with bacteriologically sterile egg fluids, this was regarded as a criterion for the presence of virus in the fluid. The fluid containing the virus was tested serologically by the complement fixation reaction against specific virus A and B sera.

The isolating experiments were supplemented by a serologic examination on serum from the second ferret passage. A sample of blood was taken from the ferret on the day of inoculation and on the fourteenth day, and was examined for the presence of complement-fixing antibodies against virus A and B.

Serologic diagnosis of influenza. Samples of blood sent in from suspected influenza cases were submitted to serologic analysis for the presence of antibodies against influenza virus A and B by means of the complement fixation test as described in previous publications (3,5).

Results.

Isolation of influenza virus. Both the ferrets which were inoculated with throat washings from the six cases of acute influenza showed typical signs of mild influenza. On the third day after inoculation their temperature rose and they showed signs of coryza. Postmortem examination was carried out on the fourth day. No pulmonary lesions were observed. In the following passages the symptoms increased slightly in severity; thus, a tem-

perature elevation already occurred on the second day after inoculation but there were no signs of pulmonary lesions. The virulence maximum apparently occurred after five to six passages, after which, for each new passage, the animals were entirely free from symptoms except for a slight temperature on the second day after inoculation. The animals were inoculated each time with an undiluted suspension of nasal mucous membrane.

The examination carried out on sera from one of the ferrets of the second passage proved that it was a question of an influenza B infection.

In the attempts to transfer the virus to eggs a result was obtained on inoculation of nasal mucous membrane suspension from the sixth ferret passage.

Chorio-allantoic fluid from the second egg passage showed weak hemagglutination and from the third a strong reaction. On complement fixation test against virus A and B sera a positive reaction for influenza B was obtained. This new strain was given the name influenza virus B strain U. Its antigenic structure in relation to the standard strain Lee is to be investigated at a later date.

Results of the examination of sera from influenza patients. The results of the serologic examinations are shown in Table 1.

Table 1.

Number of cases of influenza in Sweden established by serodiagnosis during the winter and spring of 1946.

District	Samples examined by complement fixation reaction against influenza viruses A and B											
	January			February			March			April		
	16-31			1-15			1-15			1-15		
	A	B	N	A	B	N	A	B	N	A	B	N
South Sweden....	2	11	7	10	2	6	2	1	1	6	2	
West Sweden.....				9	4							
Central Sweden....				3	6	4	20	12	5	8		
East Sweden.....		1		2	5	3	2	2	2	11	14	
North Sweden....						2	2	3	3	1	4	1
Total	2	11	8	19	11	17	25	18	5	23	28	2

A = Cases of influenza A

B = Cases of influenza B

N = Negative cases.

¹ One of the cases in the respective groups had antibodies against both virus A and virus B simultaneously.

The table demonstrates that the first cases of this epidemic were diagnosed during the second half of January. These cases occurred in the naval station of Karlskrona and in military camps in Kristianstad, two towns in the south of Sweden. Two of the patients in Karlskrona seem to have been cases of influenza A, and the others of influenza B. As subsequent developments showed, the latter type became dominant in this epidemic. A few cases of influenza A occurred during the second half of March, however, both at a military camp in Stockholm and in the form of a local epidemic in a military camp in Boden, in the northernmost part of Sweden. Two cases of influenza A were diagnosed at the end of April, one in Stockholm and one in Boden.

In the west of Sweden, the epidemic reached its peak during February, the influenza virus strain U being isolated there in that month.

Regarding the samples examined from Central Sweden, the majority came from the Örebro County Hospital which sent in samples from suspected cases at an early stage. As may be seen from the table, the epidemic did not reach this district until the end of February, and only reached its culmination during March.

In the east of Sweden, in the Stockholm area, the first cases of influenza B were diagnosed at the beginning of March, in a home for mentally defective children. The epidemic was at no time particularly widespread in Stockholm itself, but cases were diagnosed all over the city, and a fairly high morbidity rate was registered in military camps.

The cases of influenza B from the north of Sweden on which an etiologic diagnosis was made occurred in Örnsköldsvik and Boden.

In addition to examining blood samples from patients suspected of having influenza, twenty-six blood samples were also examined which were sent in to the State Bacteriologic Laboratory over the corresponding period from various parts of Blekinge, for Widal testing in connection with an epidemic of paratyphoid. Twelve of these samples contained antibodies against virus B in quantities proving that these persons had recently had an influenza infection.

Extent of the influenza epidemic according to reports from the District Health Officers. One of the duties of the health officer is to send in a report once a fortnight on cases of infectious disease including influenza that have occurred during each fourteen day

Table 2.

Occurrence of influenza in Sweden during the winter of 1946.

District	No. of cases reported every fortnight as compared with cases of influenza B established by serodiagnosis									
	January		February		March		April		May	
	1-15	16-31	1-15	16-28	1-15	16-31	1-15	16-30	1-15	16-31
ity of										
Stockholm... E										
ounty of										
Stockholm... E					158	238	138			
Uppsala E						100	95			
Söderman-										
land E						79	58	59		
Östergötland E					145	246	196	96		
Jönköping... C			108		312	302	78			
Kronoberg .. C			255		537	358	119			
Kalmar E					104	190	95			
Gotland..... E										
Blekinge S						67				
Kristianstad. S			164	279	312	133				
Malmöhus... S			71	161	325	80				
Halland..... S			94	386	657	300	58			
Bothenburg										
and Bohus W										
Älvsborg.... W			100	147	137	60				
Örebro..... C			139	254	728	248	78			
Värmland... C				170	370	126				
Drebo C				50	133	73	73			
Västmanland C					395	397	172	70		
Öpparberg... C							53			
Ävleborg... N			52		92	123	63			
Östernorr-						171	82	79		
land N										
Jämtland ... N	109	59			81	273	245			
Västerbotten N			85		71					
Norrbotten.. N					97	57	138	78	117	
					58		89			
Whole kingdom				100	185	163	74			

The incidence figures indicate the number of cases per 100,000 inhabitants. Only incidence figures for more than 50 cases per 100,000 inhabitants are given.

E = East Sweden, C = Central Sweden, S = South Sweden, W = West Sweden, N = North Sweden.

period. These reports are assembled by the Chief Health Officer of the County and forwarded to the Royal Medical Board. Extracts from these reports have been used as the basis for table 2, which will give some idea of the extent of the influenza epidemic during the winter and spring months of 1946. For many reasons, these figures only give a very relative idea of the absolute number of

cases of influenza. It has been found that the occurrence of true epidemic influenza influences these reports in such a way that the number of cases reported suddenly shows a rapid rise above a certain borderline incidence figure. Small fluctuations below this borderline do not, as a rule, indicate that genuine influenza is in progress, even though the morbidity may be fairly considerable. This borderline value has been set, on the basis of previous experience, at 50 reported cases per fourteen day period among a population of 100,000. Table 2 therefore includes only incidence figures which are the same as, or exceed, this figure.

The table demonstrates that influenza had already been reported from the province of Jämtland at the beginning of January. The actual nature of this epidemic is not known. Early in February, influenza was reported from the south of Sweden, and according to the findings from the serologic examinations this epidemic was caused by influenza virus B. The epidemic spread to the western districts during the second half of February and had reached the central, eastern and northern parts of the country by the beginning of March. The epidemic also reached its peak all over the country during the first half of March. It was more or less over by the beginning of April, for the south of Sweden, and by the end of April, for other parts of the country, but it persisted for a further fourteen days in the Västerbotten districts.

On the whole, the influenza occurred in a mild form, and the number of cases of pneumonia was not particularly large.

Discussion.

The influenza that occurred in various parts of the world during the autumn, winter, and spring months of 1945—46 was, in general, influenza B. Although the epidemics were widespread, the cases were everywhere mild, from the clinical standpoint. The areas affected were in most instances fairly well restricted, and were generally confined to one country or to one particular part of the country. The paths of infection were difficult to follow; no spread from country to country or from continent to continent could be observed, and from the point of view of infection the various areas involved seem to have existed fairly independently of one another.

The Swedish epidemic had one characteristic worthy of mention. It spread over the country at a surprisingly slow rate. A whole

month elapsed, after the outbreak of the epidemic, before it reached Stockholm, for instance. Because of this fact, its existence and etiology was, fortunately, known for quite a long time before it reached its peak. If the possibilities had been at hand, vaccination of nursing and hospital staffs in Stockholm could, for instance, have been undertaken in plenty of time before the outbreak of the epidemic. A good system of defence against influenza thus requires that there shall be the possibility for a diagnosis of the first cases occurring in the country, and this in its turn is only possible if an effective reporting system has been built up.

With regard to the latter, our investigations brought out certain defects in the present system. Thus, it will be seen that in Blekinge, for instance, where the first cases were diagnosed and where an investigation in adjoining areas revealed that influenza had been fairly extensive throughout the province, no particularly high incidence of influenza was reported during the entire period.

Summary.

A report is made on the 1946 influenza epidemic in Sweden. Influenza B dominated in this epidemic, but a few cases of influenza A also occurred. In most instances the cases were mild, from the clinical standpoint. A Swedish strain of the influenza B virus was isolated. Certain characteristic features of the epidemic and their consequences are discussed.

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Idiopathic Familial Hyperlipemia Attended with Hepato-Splenomegaly.

By

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Lipidoses comprise a group of diseases, partly hereditary, characterized by intra- and sometimes also extra-cellular deposition of lipids and caused by disturbances of the intermediary lipid metabolism.

These diseases have been classified somewhat differently by the different authors. The main groups are as follows: (1) Gaucher's disease (cerebroside), (2) Niemann-Pick's disease (sphingomyelin), (3) xanthomatosis (cholesterol). As a rule Schüller-Christian's disease is classified with the last-mentioned group, but recent investigations by Engelbreth-Holm, Teilum & Erna Christensen indicate that it is a question of a disease of a different nature.

Of these 3 main groups, xanthomatosis has been attracting more and more attention during latter years. This group, to be dealt with in more detail below, is met with in two forms, primary, essential and secondary, symptomatic. In both groups, which should be kept sharply separate, the characteristic lipid is cholesterol — histologically appearing in the form of the so-called foam cells.

Primary, essential xanthomatoses are hereditary, dominant affections presenting themselves as xanthelasmata, xanthomata, arcus senilis, and cholesterol deposits in certain internal organs. Serum cholesterol is usually elevated, whereas neutral fat and phospholipid are only slightly or not at all increased. For this reason a lipemic (milky) blood serum is hardly ever encountered

in these patients. Thannhauser also sets up a so-called normo-cholesterolemic group under which he classifies osseous xanthomata, xanthomatosis of the lungs, liver and spleen, and lastly Schüller-Christian's disease. As mentioned above, it is, however, doubtful whether the last-mentioned disease may be classified with xanthomatoses.

Among cutaneous manifestations xanthelasmata and xanthomata are well known. More rarely one meets with a disseminated form consisting of darker, confluent xanthoma elements, also present on the mucous membrane of the mouth and pharynx.

Deposits in the blood-vessels (coronary arteries, C. Müller, Harbitz) are of the utmost importance because of their frequency and serious consequences. More rarely one encounters deposits in the biliary tract which may cause the so-called xanthomatous, biliary cirrhosis (Riisfeldt-Pedersen, Thannhauser) characterized by violent jaundice, enlargement of the liver and spleen and enormous hypercholesterolemia without a milky serum. Deposits in the pancreas, liver, spleen, and lungs do occur, but only in rare cases.

Little is known of the etiology of primary, essential xanthomatosis apart from the presumption that it is a question of disturbance of intermediary lipid metabolism. The amount of cholesterol in the blood alone does not appear to be a decisive, but sooner a predisposing factor in the formation of xanthoma (M. Faber). Thannhauser and Magendanz advance the theory of an intracellular disturbance of metabolism in the reticular cells and histiocytes in contradistinction to the secondary xanthomatoses in which cases the lipid is thought to be phagocytized by these cells by which action the foam cells arise.

Secondary, symptomatic xanthomatoses differ in several ways from the primary ones. They do not constitute a pathological entity. The xanthoma elements appear as a symptom of hyperlipemia with which they may arise and subside. A prominent symptom, present in the majority of cases, is a *lipemic (milky) serum*, due to an increase in the neutral fat contained in the serum. This increase may become extremely marked, while there is no corresponding increase in cholesterol. This is an important and practical means of differential diagnosis from primary xanthomatosis which hardly ever gives a milky serum. This has been strongly emphasized by Thannhauser. Moreover, foam cells are more rarely met with in cases of secondary xanthomatosis where

the cholesterol is more often of an extracellular situation. The skin manifestations are also different, usually appearing in the form of the so-called eruptive, papular xanthoma. At the same time, deposits in the liver and spleen are more frequent.

Secondary xanthomatosis due to hyperlipemia may attend the following diseases: Diabetes mellitus, chronic pancreatitis, von Gierke's disease, nephrosis, and idiopathic familial hyperlipemia with hepato-splenomegaly. This paper does not pretend to deal with the cause of hyperlipemia (primarily appearing in consequence of an increase in neutral fat) in each individual case. It should only be mentioned that factors to be considered are disturbance of carbohydrate metabolism, defective removal of fat from the blood, and the so-called transport hyperlipemia.

Furthermore, secondary xanthomatoses may arise in connexion with all conditions attended with an increase in serum cholesterol, if the increase is of sufficient extent and duration.

Regarding the normal content of the various fat fractions in the blood serum, the writer will just state the following: While the total content of cholesterol remains fairly constant in the same individual, independent of the intake of food, the neutral fat is subject to considerable alimentary fluctuations (Nissen). Serum for the determination of neutral fat should therefore always be taken fasting. The normal content is stated to be 400—600 mg per cent. After the intake of a high fat meal it will rise to a maximum in the course of 4—5 hours. A persistent hyperlipemia is however, always a sign of abnormal metabolic processes in the body.

According to Kornerup a total cholesterol of 250—300 mg per cent is a slight or doubtful increase. A figure above 300 mg per cent is definitely pathological.

Neutral fat and lecithin are usually elevated at the same time whereas cholesterol does not always attend them.

After this brief survey of lipidoses, the writer will go on to describe a peculiar case which gives occasion to considerable diagnostic contemplations:

The patient is a 16-year-old young man (family history below). He has been delicate almost from birth. Has had measles and whooping cough. At the age of 7 he had an attack of «rheumatic fever» with violent articular pain and high fever. It was attended with jaundice which however, quickly subsided. He has always been suffering from fatigue. Unable to stand exertions which immediately cause dyspnoea and

pressure feeling in the chest. Moreover, there has frequently been pain of short duration in the abdomen, particularly the left side. For about 6 months prior to admission there had been symptoms of colitis with slimy, sometimes watery stools.

First admission to this department in 1945, at the age of 14, mainly because of the colitis.

On admission he was not debilitated. Small for his age, 134 cm tall, exhibiting considerable adiposity, particularly localized to the abdomen, mons veneris, and breasts. The genitals were poorly developed, but the testes had descended to the scrotum. On the whole, the patient was the picture of adiposo-genital dystrophy. Otherwise the physical examination showed nothing abnormal and the heart was of natural size. Still, the pulse was always somewhat accelerated. Tension: 110/70. Abdomen soft, no enlargement of the liver or spleen.

X-ray of the skull showed a normal sella turcica, ophthalmological examination normal. X-ray of the lungs showed normal pulmonary fields.

Laboratory tests: Urine -:- + albumin, pus, and sugar. Hemoglobin 103 per cent. Erythrocytes 4.5 mill., leucocytes 6,500. No immature forms. Wassermann -:- +. Blood sedimentation rate 75—48 mm per hour. Fasting blood sugar 83 mg per cent.

During his stay in hospital there was epistaxis a few times. Gradual improvement of the colitis without special diet. For the adiposo-genital dystrophy he was treated with chorionic gonadotropin in rather large doses with a distinct effect on the genitals.

After discharge from hospital he tried various easy jobs, but each time he had to give up because of fatigue. The symptoms of colitis returned, and he felt weak and unwell. His cardiac symptoms, however, seemed to have subsided.

Second admission at the age of 16 (1946).

At this time he is still rather small, 140 cm, but the adiposo-genital dystrophy is considerably less marked and the genitals better developed, but still rather infantile. No pubes or hair. Now he looks more somewhat like patients with pituitary dwarfism. (See the fig.)

The skin is natural without jaundice, hemorrhages, xanthelasmata or xanthomata. Otherwise the physical examination corresponded to the earlier findings apart from a distinct enlargement of the liver the margin of which could be felt immediately below the costal border. The spleen is not palpable, but the dullness without a doubt increased.

There is a certain tendency to hemorrhage. His nose bleeds easily and there was considerable bleeding from a cut in the ear. No cutaneous hemorrhage. Marked colitis with slimy, watery stools.

A routine blood sample revealed that *his serum was absolutely milk-white* both fasting and after meals. Repeated tests confirmed this peculiar finding.

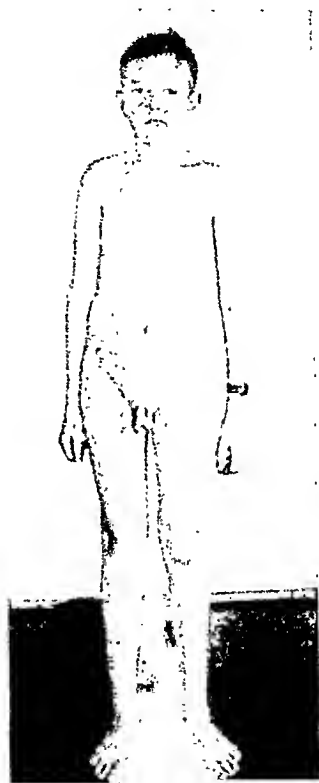
Physical examination: Height 140 cm, weight 32.5—37 kg.

Blood tests: Hemoglobin 100 per cent. Erythr. 4.6 mill. Leucocytes 9,300. No immature red or white blood corpuscles.

Thrombocytes 323,000—170,000—184,000—243,000.

Bleeding time 10 min. Clotting time 5 min., prothrombin index 109. Fasting blood sugar 115 mg per cent. Blood sugar tolerance test with 32 g glucose: Rising to 149 mg per cent. in an hour. Normal fall. Serum proteins: Total protein 8.5 per cent., albumin 5.8 per cent., globulin 2.7 per cent.

Serum calcium 13.4 mg per cent. Serum phosphorus 6.1 mg per cent. Serum phosphatase 9.1 units (norm. 3.1—9.1). Blood sedimentation rate 45—26 mm per hour.



16-year-old boy with idiopathic, familial hyperlipemia and hepato-splenomegaly. In addition infantilism and dwarfism.

Blood urea: 18 mg per cent.

Urine analysis: Daily output of urine and specific gravity showed nothing striking. No albumin, pus, or sugar in the urine. Repeated tests failed to show acetone or diacetic acid in the urine. No diastase reaction.

Faeces contained no blood. Fat analysis showed: Total fat 10.3 per cent of dried faeces (norm. below 35 per cent). Neutral fat 64 per cent of the total fat (norm. below 35 per cent). Split fat 36 per cent of the total fat (norm. more than 65 per cent).

X-ray of the skull, thorax, bones, and colon showed nothing abnormal. Sternal punctate showed a somewhat increased erythropoiesis and eosinophilia, but foam cells could not be detected.

Metabolic rate: 102—117 per cent. Electrocardiogram during rest and during anoxemia experiments showed nothing abnormal.

For the purpose of elucidating the nature of the hyperlipemia, analyses were made of the various fat fractions in the serum on varying diets.¹ The result may be seen from Table 1. All blood samples were taken fasting.

Table 1.

Blood lipid analyses in a case (16-year-old boy) of idiopathic hyperlipemia on various diets.

Serum mg %	Normal hospital diet	Low fat 1 month	High fat 14 days	High fat 1 month	Normal diet at home 1½ month	Normal 16-year-old boy
Total lipid	3,840	3,080	3,405	4,100	9,935	815
Phospholipid	573	520	619	744	1,200	187
Total cholesterol...	596	483	492	680	968	222
Free cholesterol...	204	229	215	301	393	80
Neutral fat	2,671	2,077	2,294	2,676	7,767	406

The only fat contained in the low fat diet was about 100 g of vegetable margarine daily — a diet which is by no means severe and which the patient could stand easily for a long time. The high fat diet contained 250 g of butter daily and the amount of cream and milk the patient could take. We succeeded in keeping the patient on this diet for a month. After a month's stay at home on ordinary diet his serum lipids were again analysed.

It is apparent from the table that all the analyses showed an elevation of all lipid fractions, but most of the neutral fat, as was to be expected considering the milk-white colour of the serum. Furthermore, it is interesting to note the fluctuations in the lipids, and especially in the neutral fat, brought about by a change of fat content in the diet. — Immediately after the high fat period the total lipids were 4,100 mg per cent. This figure does not seem particularly high considering the enormous daily amount of fat

¹ All lipid analyses were made by "Medicinsk Laboratorium", Copenhagen, Chiefs: E. Bierring, M. D., and E. Nielsen, M. D.

Methods of analysis:

Total lipid: Schoenheimer & Sperry (*J. Biol. Chem.* 106—745—1934.)

Phospholipid: Gudrun Bruu (*Bibliotek f. Læger* 131—197 and 203—1939.)

Cholesterol: Georg Brun (*Hospitalstidende* 78—688—1935).

ingested by the patient for a whole month. Six weeks later the total lipids were, however, 9 935 mg per cent. Considering that this was by far the highest value found at any time, the rise must without a doubt be a consequence of the high fat diet which thus appears to have a rather protracted effect on the serum lipids.

An exceedingly interesting feature is the behaviour of the liver and spleen during the diets: Following the low fat diet it was no longer possible to demonstrate an enlargement of the liver, and its margin could not be felt below the costal border. The increased spleen dullness had also disappeared. During the high fat diet the liver and spleen again acquired their former size.

Ophthalmoscopy was performed repeatedly, in the beginning without any abnormal findings. Towards the end of the high fat period (total serum lipid about 4 per cent), however, distinct eye-ground changes were found and described as follows: The arteries present themselves with a very broad reflex of light and a peculiar yellowish orange colour. Corresponding changes may be seen on a few peripheral veins. Diagnosis: Lipemia retinalis.

During the entire 4-months stay in hospital the patient was feeling well. Now and then he had some vague feeling in the abdomen, but there were no attacks of pain, not either while he was on high fat diet. The muddy, milky appearance of the serum remained unchanged apart from slight fluctuations in its intensity. His general condition was good, and the symptoms of colitis abated. He tolerated the various diets well. For some time (from Dec. 6th 1946—Jan. 18th 1947) he received thyroid hormone (tabl. gland. thyr. No. 1, one tablet three times daily). It was administered in the hope of reducing the serum lipid. It is impossible to say whether the hormone was of any effect, as it was given chiefly during the low fat period. The intestinal disorder was treated with vitamin B. in large doses.

Summary of the Case: A young man, aged 16, who has been delicate from birth and who exhibits signs of adiposo-genital dystrophy, infantilism and reduced growth of the pituitary type, is found to suffer from enlargement of the liver and spleen. A routine blood sample revealed considerable hyperlipemia with a muddy, milky serum due to an increase of neutral fat. The other fat fractions are not elevated correspondingly. Low fat and high fat diets bring about a fall and rise in the neutral fat and a decrease and increase in the size of the liver and spleen. Lipemia retinalis is found at a time when the fat level is highest. There are

no skin manifestations. In addition, the patient is suffering from colitis and mild hemorrhagic diathesis following thrombopenia. The general condition is good, but the serum remains milky, and the patient tires even after light work.

Discussion: The most peculiar symptoms in the case described above are: Hyperlipemia and hepato-splenomegaly.

When looking for the cause of the hyperlipemia, one can at once eliminate some of the diseases mentioned in the introduction: Diabetes mellitus, nephrosis, and von Gierke's disease. The last-mentioned condition is also attended with enlargement of the liver as in our patient, but the other symptoms like ketonuria, hypoglycemia, and cardiac hypertrophy were absent. Other causes of hyperlipemia: Disorders of the liver (obstructive jaundice, phosphorus, alcohol, chloroform, ether, and arsenic poisoning), starvation, anemia, and Niemann-Pick's disease can also be ruled out at once.

A symptom of Gaucher's disease, also found in our patient, is hemorrhagic diathesis, but its predominant symptom is splenomegaly, and milky serum is never encountered. In addition, foam cells were not demonstrable in the sternal punctate in our case.

Hormonal disorder could hardly be imagined to cause the syndrome. In cases of hypogonadism and in castrates, Teilum has found a moderate increase in serum cholesterol, but lipemic serum has not been reported. Signs of myxoedema are not demonstrable in our patient.

Acute as well as chronic pancreatitis may be attended with considerable hyperlipemia, but in addition there are often symptoms of diabetes. Enlargement of the liver and spleen is rare. Frequently there are attacks of pain in the abdomen, attended with fever. During such attacks there will be increased diastase in the urine.

There is not much to indicate that our patient is suffering from a disorder of the pancreas. This possibility is also contradicted by the familial occurrence of the disease (see below).

Since the cause of the hyperlipemia is not detectable among the above-mentioned, generally known diseases, the case presumably belongs to the rare group of idiopathic hyperlipemia. And the syndrome does resemble the one described by Thannhauser as idiopathic, familial hyperlipemia with hepatosplenomegaly. Cases of this extremely rare disease appear to have been reported only by: Bernstein et al., Bürger & Grütz, Goodman et al., Franklin,

Holt et al., and Opitz, a total of 6 cases (collected by Thannhauser).

In all cases the patients have been children. The disease has usually been revealed by a routine blood sample showing the milky serum. The children are usually rather poorly developed, but not thin or cachectic. There is a moderate enlargement of the liver and spleen. Blood tests show violent increase in neutral fat, whereas the other fat fractions are only moderately elevated. The lipid level may be affected by the diet, and the enlargement of the liver and spleen fluctuates with the fat content of the diet. Still, the hyperlipemia cannot be completely overcome, neither by dietetic measures nor any other means, and the serum retains its milky appearance. Lipemia retinalis is stated to occur when the fat level of the serum reaches 2.5—3 per cent. In our case this symptom could not, however, be produced, until it reached 3.5—4 per cent.

Some of the cases have suffered from a peculiar acute abdomen, resembling acute appendicitis, pancreatitis or peritonitis. According to Holt et al. these attacks, which occurred in the cases reported by Holt, Opitz, and Bernstein, are preceded by a rise in the lipid level of the blood. When the latter has reached 7—8 per cent, the attack will occur in a few hours. There is high fever, violent abdominal pain and engorgement of the superficial abdominal veins.

Following such an attack, which lasts for 2—4 days, a considerable enlargement may be felt of the liver and spleen, and the lipid level of the blood has fallen to lower values. The cause of the attacks is unknown. A laparotomy during an attack in Holt's case failed to reveal anything abnormal. Our patient suffered from abdominal pain, but the writer is not prepared to say with certainty whether it was a question of attacks like those reported in the literature. High fat diet did not produce attacks in our case.

Table 2 gives a survey of the serum lipid analyses in the case reported up to now.

Skin manifestations of the eruptive, papular, xanthomatous type were present in several of the cases. They may be seen all over the body, particularly on the extensor surfaces of the extremities and on the buttocks, but they may also occur on the lips, palate and like tophi on the ears. Low fat diet may bring them to subside completely. Like our patient, the cases reported by Opitz and Franklin did not exhibit cutaneous symptoms.

Table 2.

Blood lipid analyses in the reported cases of hyperlipemia and hepatosplenomegaly. Several of these cases have secondarily xanthomatosis.

mg per cent	Bürger	Opitz	Franklin	Holt	Bernstein	Goodman	Writer's case
Total lipid	9,476	1,880	3,540	7,370	7,430	3,954	3,840
Total fatty acids	—	—	—	—	—	3,115	2,671
Total cholesterol	686	283	188	329	1,059	379	596
Free cholesterol	315	165	—	127	677	158	204
Ester cholesterol	316	98	—	202	362	220	392
Total phosphatides...	1,740	358	—	430	941	465	573
Lecithin	—	—	—	—	—	452	—
Cephalin	—	—	—	—	—	Traces	—
Sphingomyelin	—	—	—	—	—	12.6	—

Disturbances of endocrine function have not been described earlier. One might be tempted to believe that the adiposo-genital dystrophy and considerably reduced growth in our case is due to deposition of lipids in the pituitary with a consequently reduced production of hormones, as is seen in Schüller-Christian's disease.

Colitis and hemorrhagic diathesis have not either been reported before. According to Thannhauser the stools are normal without increased fat content. We found a normal content of total fat, but an increase in the neutral fat fraction. Evidently, the hemorrhagic diathesis is due to a mild thrombopenia.

Familial occurrence of the disease has been demonstrated by Holt et al. who found enlargement of the liver and spleen attended with an increase in serum lipid in several members of their patient's family.

We have obtained the history of our patient's parents and all 4 siblings.

First we shall deal with his 2 brothers. Both died while still young. Their history has been obtained partly from this Department, where they have both been treated, partly from other hospitals and the parents:

The eldest brother is stated to have developed normally up to the age of 5 when he had jaundice. Since then delicate with a tendency to attacks of catarrhal inflammations and anemia.

Admitted to this Department at the age of 12 (1930), because he had been ailing and tired for the last 2 months and had frequent, slimy stools. No history of abdominal pain or fever. On admission he was pale and weak, small and slender. Height 129 cm, weight 23 kg.

Abdomen strikingly large and broad, but without signs of ascites.

Great enlargement of the liver which reaches 7 cm below the costal border. Spleen not palpable, but the spleen dullness is increased. No enlargement of lymph glands and no oedemata. Stethoscopy of heart and lungs normal. Skin normal without jaundice. No mention of xanthelasmata or xanthomata.

No tendency to bleeding.

Laboratory tests: Urine normal. Hemoglobin 62 per cent. Erythr. 3.2 mill. Leucocytes 4,200. Clotting time 5 min. Bleeding time $3\frac{1}{2}$ min. Thrombocytes 675,000. No immature red or white blood corpuscles. Icteric index (Meulengracht) 9. Wassermann \div —. Kahn \div —.

The case record states explicitly that there was a *distinct fat colouring of serum* taken immediately before a meal, but regrettably no analyses were made.

During his stay in hospital there was some improvement in his condition. Hemoglobin rose to 73 per cent, and the weight to 26.8 kg. The symptoms of colitis subsided partly.

Moreover, it is stated that he was small for his age up to 14, but after that he attained normal height. From the age of 14 he suffered from a disease in the back. He could not stay upright and had to wear a supporting corset. In addition, yellow spots and nodules appeared on the ears, back of the hands, and the knee-caps. The size of the nodules was subject to fluctuations, thus they grew when he had attacks of »rheumatism» which he acquired at the age of 21. When 18 years old he had an attack of pain in the abdomen and was hospitalized with symptoms of appendicitis, but no operation was made. At the age of 24 he was hospitalized again and the following diagnoses were made: Lipemia, enlargement of the liver, rheumatoid arthritis, scarlet fever, chronic nephritis, arterial hypertension, kyphosis dorsalis (Scheuermann), mild infantilism.

This time a sternal puncture was made, revealing an extremely cellular bone marrow, normal in all respects apart from a single foam cell. In spite of energetic search, no more foam cells could be found.

At this time the liver was 4 finger-breadths below the costal border. The spleen was impalpable.

His general condition grew constantly worse. A couple of times he had violent epistaxis, but showed no other signs of a tendency to hemorrhage. He had never been capable of more than quite easy work and died in his home at the age of 27. There is no definite information about the cause of death.

Summary of the Case: Eldest brother of our patient. Delicate from the age of 5, showing symptoms of colitis. At the age of 12 a finding was made of a considerable enlargement of the liver and spleen and a *muddy, milky serum*. Later he developed yellow spots and nodules on the ears, back of the hands, and knee-caps. These nodules varied in size. Now and then abdominal pain. No definite tendency to hemorrhage. The sternal punctate contained only one foam cell, otherwise nothing abnormal. He remained

infantile with considerable enlargement of the liver and spleen, and growing more and more debilitated, he died at the age of 27.

His second brother had also been delicate from birth. Is said to have had a »big stomach» always. From the age of 5 he began to suffer from epistaxis of increasing violence. In spite of various treatments, the nose bleeding persisted, and at times he was extremely anemic. The family doctor is said to have observed petechiae, but no major subcutaneous hemorrhage or hematuria. Neither had any jaundice been observed.

At the age of 6 (1926) he was admitted to this Department. On admission he is pale and marked by rickets. His skin is normal without jaundice, xanthelasmata, xanthomata, petechiae, or suggillations.

The abdomen is large and broad, most prominent on the right side, where *the liver is considerably enlarged*, about 3 finger-breadths below the costal border. As to the spleen, no definite enlargement can be felt. Stethoscopy of the heart and lungs shows nothing abnormal. No enlargement of lymph glands.

Laboratory tests: Urine: \div — albumin, \div — sugar. Hemoglobin 39 per cent. Erythrocytes 3.98 mill. Leucocytes 9,600. No immature red or white blood corpuscles.

Thrombocytes 95,800. Bleeding time more than 16 min. Clotting time $3\frac{1}{2}$ —4 min. Osmotic resistance nat. Icteric index (Meulengracht) 5. Wassermann \div —.

Unfortunately, no mention is made of the colour and fat content of the serum.

No symptoms of colitis.

During the stay in hospital he had epistaxis several times, but gradually the attacks became less frequent. The hemoglobin percentage rose to 90, the bleeding time fell to 8 min., and upon discharge he was feeling comparatively well.

After his return home, his condition was again aggravated and the epistaxis recurred.

There was no jaundice, xanthelasmata or xanthomata. Following a steady downhill course he died at the age of 8.

The cause of death was stated to be pneumonia.

Summary of the Case: A second brother of our patient. Always delicate with a »big stomach». From the age of 5 attacks of epistaxis with increasing frequency. At the age of 6 (1926) the liver is found to be considerably enlarged, but not the spleen. Prolonged bleeding time, thrombopenia, and anemia. No skin manifestations.

Unfortunately, no mention is made of the colour and fat content of the serum.

Increasing hemorrhagic diathesis and death at the age of 8.

The father (aged 56) is healthy and looks after his work as a country postman. He has a typical flat xanthelasma in the vicinity of one eye.

The mother (aged 51) is healthy.

The eldest sister (aged 23) is said to have suffered from fatigue always. She has been treated with heliotherapy and medicaments without any effect. No enlargement of the liver or spleen.

The youngest sister (aged 9) is said to have exhibited symptoms resembling those of colitis. She is normally developed and there is no enlargement of the liver or spleen. Table 3 gives the result of the clinical examination of the parents and sisters and brothers, also setting out the serum lipids in those still alive. For comparison, a normal person, chosen at random, is recorded, at the bottom.

Table 3.

The family of a 16-year-old boy with idiopathic hyperlipemia and hepatosplenomegaly.

Ago	Total lipid	Phospho-lipid	Total cholesterol	Free cholesterol	Neutral fat	Remarks
Father.... 56	1,480	213	390	143	877	Xanthelasma on the corner of the eye
Mother ... 51	1,590	281	345	123	954	Lipemic serum. Hepato-splenomegaly. Xanthomata. Colitis. Infantile.
Brother... †27	1,235	294	310	132	631	
Brother... †8	—	—	—	—	—	Hepato-(splenomegaly). Hemorrhagic diathesis.
Sister..... 23	1,460	213	311	115	936	Normal person, chosen at random
Sister..... 9	1,200	175	349	100	676	
Control ... 43	1,010	206	237	99	567	

As apparent from the details obtained about the patient's family, his 2 brothers have exhibited an exactly similar syndrome.

In addition, one of them has had a rather marked xanthomatosis, without a doubt belonging to the secondary type, where the elements may be seen as tophi on the ears as in this case.

The other members of the family are healthy, but the serum lipid tests show that all of them are affected with a slight increase in total lipid and neutral fat. Total cholesterol is also slightly elevated, especially in the father who also exhibits a flat xanthelasma in the vicinity of one eye, similar to what is met with in cases of primary, essential xanthomatosis.

In this lipidosis family 2 of the sons suffered from idiopathic hyperlipemia attended with enlargement of the liver and spleen (and secondary xanthomatosis in the one case). The 3rd son also exhibited hepatosplenomegaly, whereas no information can be obtained as to the colour of the serum. In his case hemorrhagic diathesis in consequence of thrombopenia was more prominent than in the others. The 2 daughters and the mother are found to exhibit slight changes in the serum lipids, but no other distinctly pathological symptoms. Possibly the father is suffering from essential xanthomatosis, but he too exhibits a slight increase in total lipid and neutral fat.

So far the etiology of the disease is absolutely unknown. Holt et al. tried to elucidate the pathogenesis by numerous experiments. Insulin, anterior pituitary hormone, thyroxin, and liver extracts failed to affect the hyperlipemia. The same authors are of opinion that a hormonal factor in the blood regulates the lipids. Transfusion with normal blood was also without effect. In Goodman's case there was no lipase in the blood. This abnormality, which Thannhauser attributes with a certain etiological importance, has not been demonstrated in other cases.

The treatment must be dietetic. As mentioned above, a low fat diet can reduce the lipid content of the serum and bring the enlargement of the liver and spleen to subside.

Earlier authors state that the prognosis is favourable, but no case has been observed for any length of time. Considering that the enlargement of the liver and spleen is reversible, there can hardly be any major damage to the parenchyma of these organs. On the other hand, the disease will without a doubt predispose its victim to atherosclerosis.

Of our 3 cases 2 died while still young and the third one is delicate, dwarfish, infantile and unable to carry out any major manual labour. This would indicate that the prognosis is hardly as favourable as earlier authors have been inclined to think.

Summary.

After giving a short survey of lipidoses with a special view to primary and secondary xanthomatoses in which particular attention is drawn to the significance of lipemie (milky) serum, the writer reports a case in a 16-year-old boy exhibiting the following

syndrome: Hepatosplenomegaly, hyperlipemia with milky serum, colitis, hemorrhagic diathesis, and hormonal symptoms (dwarfism and adiposo-genital dystrophy). Serum lipid analyses show a violent increase in neutral fat, but only moderate elevation of total cholesterol and phospholipid. Low fat and high fat diets bring about a fall and rise in neutral fat (see Table 1). The enlargement of the liver and spleen subsides on low fat diet, in order to return on high fat diet which, in addition, produces lipemia retinalis.

Reviewing the ordinary known causes of hyperlipemia, the writer arrives at the conclusion that the case is to be classified with idiopathic familial hyperlipemia with hepatosplenomegaly as described by Thannhauser. A further description is given of this disease which only appears to have been reported in the literature in 6 cases (see Table 2).

A family investigation reveals that the patient's 2 brothers have suffered from the very same disease. One of them had a quite marked xanthomatosis, evidently belonging to the secondary type. A prominent symptom in the second brother was hemorrhagic diathesis in consequence of thrombopenia. Both died while still young (27 and 8 respectively). Serum lipid analyses in the case of the parents and 2 sisters (see Table 3) show a slight increase in total lipid and neutral fat in the mother and 2 sisters who are otherwise healthy. Total cholesterol is also slightly elevated, particularly in the father who, in addition, has a typical flat xanthelasma in the vicinity of one eye. Therefore, he is possibly suffering from primary essential xanthomatosis.

The etiology of the disease is unknown. The treatment is dietetic, the enlargement of the liver and spleen subsiding on low fat diet which also reduces the hyperlipemia. Still, the serum retains its milky appearance.

The prognosis is stated to be good, but so far no case has been observed for any length of time. This statement appears to be contradicted by our cases in which 2 out of 3 died while still young

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On the Intradermal Salt Solution Test in Forming Diagnostics of Edema.

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The indication of the latent or beginning edema is of a certain interest as, according to Widal, 5 kg of water may be found in the body as edema without it being possible to palpate it.

The changes of the elasticity of cutis and subcutis, caused by edema and inflammation and perceptible at palpation, have been graphically recorded by Schade by the aid of his elastometer. This apparatus works in the following way. A rod rests perpendicularly on the skin. This rod is loaded and unloaded and the movement of the rod is recorded by a cymograph. By the elastometer Schade could indicate changes in elasticity smaller than those palpable with the finger. He mentions, however, that changes in elasticity are not necessarily due to abnormal content of water.

In order to indicate latent edema in heart-diseases Kaufmann made an experiment, where decrease of the hydrostatical pressure was meant to cause edema to disappear. The patient, in bed and fasting, had to drink 150 ml of water during each of 6 hours in succession, and the secretion of urine was controlled. During the last two hours the foot-end of the bed was raised. If the diuresis increased he concluded that there was latent edema in the legs.

By later examinations Guggenheimer and Hirsch have found that the test does not give reliable results. Moreover it is both time-consuming and troublesome.

When in 1923 Aldrich and McClure described their intradermal salt solution test there was obtained an objective measure of

Following edema already developed and a manner of indicating minor ones. They injected 0.2 ml of a 0.8 per cent NaCl solution intradermally in two places with an interval of 2 cm between the injections. The papules formed gradually disappeared, and the time until they were no longer palpable was measured (below to be called the disappearance time). Aldrich and McClure stated the normal disappearance time in 12 experimentees, both persons in good health and patients with fractures (age ranging from one to adult). They found it to be between 50 and 103 minutes. In patients suffering from nephritis with edema but without signs of cardio-vascular disease they noticed that the papules disappeared within a fairly short time, varying from a few seconds to 17 minutes. They found this method appropriate as a means of following the changes of edema. »Since the disappearance time sharply decreases coincident with or preceding the development of edema, and increases with or before the subsidence of edema we have been able to use the curve of the disappearance time as an index of the tendency to increasing or decreasing edema and as a means of ascertaining a return to normal.»

Similar discoveries were made by Guggenheimer and Hirsch. Reifschneider confirmed Aldrich-McClure's discoveries in nephritis.

A shortened disappearance time has later been observed in several diseased conditions, such as toxical cases of scarlatina and diphtheria (Baker), toxicosis gravidarum and thyreotoxicosis (Mora). A shortened disappearance time has been found in children suffering from pneumonia (Harrison) and insufficiencia cordis with edema (Olmsted). In children with diarrhoea and signs of desiccation Schauer found an increased disappearance time. In children Leonhardt as well as Beck and Schauer found a physiological lengthening of the disappearance time with increasing age.

The disappearance time in vascular diseases has been studied by Cohen et al., who found a decreased time in impending gangrenes and contiguous to gangrenous regions. Kunde has compared the intradermal salt solution test with the elastometer test according to Schade, and she found that the intradermal salt solution test was more sensitive to changes in the water content of the skin.

In order to establish the existence of impending edema Eisner and Kallner modified the experiment so that the test was carried out on the leg in horizontal, suspended and elevated positions.

In patients with deranged water balance was found a decrease of the disappearance time in suspended positions compared with horizontal positions. A considerably shorter disappearance time was observed by Recht within lipomatous parts in persons belonging to the hydrolipomatous constitution. Appel and Brill as well as Hopps and Christopher consider it possible to discover a postoperative dehydration by a decreased disappearance time.

The material described has generally been scant and there are no particulars as to the limits of the errors inherent in the methods. Sometimes the disappearance time has been given in fractions of minutes, an accuracy that is probably impossible to reach. Different examiners have used different fluids. Thus NaCl solutions of 0.8, 0.85, and 0.9 per cent have been used. Some examiners prefer normosal solution, others Ringer's solution.

The Author's Experiments.

A renewed examination of the clinical value of the intradermal salt solution test has been made by the author. In the course of experiments different injection solutions have been tested on adults without symptoms of disease.

With a syringe, graduated in 0.10 ml and equipped with a needle nr 20, 0.20 ml of a 0.8 per cent sterile NaCl solution is injected intracutaneously, after the skin has been cleaned with a cotton sod dipped in alcohol. You must be very careful not to put the needle too deep. It should be dimly seen through the skin. When the injection is made in the right manner you feel a certain resistance. If the injection is made too deep, in the subcutis, the resistance is less. After a correct injection there is to be seen a pale papule, where the pores of the skin are discernible as small hollows. The papule at first decreases somewhat in height, but at the same time it spreads out. It gradually becomes flatter and flatter, until finally it disappears. The disappearance time is best ascertained by palpation; you pass your finger softly over the spot, where the injection has been made. To begin with the reading off ought to be made every 5 minutes; later when the papule is scarcely palpable, every minute. If there is reason to believe that the disappearance time will be short the readings off must be made oftener already from the beginning. You must not be deceived by the little traumatic elevation of the epithelium caused by the insertion of the needle. At the experiments carried

out by the author the registration has been made so that values within the first half of a minute are referred to the next lower figure, whereas values within the latter half of a minute are referred to the next higher figure.

Reading off Errors.

It is of course difficult to get exact values in a case like this, where without the aid of recording instruments the subjective judgment so immediately influences the reading off. We must take into consideration the examiner's capability to estimate his own actual pressure of palpation and to feel the small inequalities on the surface of the skin just before the disappearance of the papules. When sense-organs are to record irritations the exhaustibility of the examiner plays an important part as well as his tiredness and these circumstances are of course applicable in this case. It is a matter of fact that the judgment is facilitated, if the skin examined has as smooth a surface and as homogeneous a consistency as possible.

In order to get an idea of the size of the errors in connection with the readings off, experiments were made in the following manner (when after training the examiner considered himself capable to make the readings off as uniform as possible). In as homogeneous a cutis as possible on the volar side of the forearm 10 healthy experimentees got 2 injections each with the papules desired as results. The injections were made with a distance of 10 cm, so that the papules should not influence each other. The interval between the injections varied from 10 to 60 minutes. The readings off were made without the examiner seeing the watch, the time being recorded by another person. The times read off varied between 45 and 60 minutes. A difference of 3 minutes between the readings off in the same person occurred twice, a difference of 4 minutes 4 times, 5 minutes twice, and 6 minutes twice. The standard error of the differences (σ) = ± 4.5 minutes and the standard error (σ) of one single determination = ± 3.2 minutes, and $\varepsilon(\sigma)$ = ± 0.71 . In order to see if the standard errors became less, when the disappearance times decreased analogous experiments were made in edematous persons within their edematous parts. The disappearance time varied between 7 and 15 minutes. A difference of 1 minute occurred once, 2 minutes twice, 3 minutes 5 times, and 4 minutes once. The standard error of the

differences (σ) was ± 2.7 minutes, and the standard error of one single determination was ± 1.9 minutes and $\epsilon(\sigma) = \pm 0.42$.

Different Injection Solutions.

The disappearance times were compared, different injection solutions being used: 0.8, 0.85, 0.9 per cent NaCl solution and Ringer's solution (Pharmac. svecica Ed. X). The test was made so that on 10 healthy experimentees injections of 0.2 ml of each solution were made, one on each calf of the leg. As to disappearance times no decided difference between the different solutions was possible to observe.

The Disappearance Time in Healthy Persons.

For the experiments mentioned below 0.8 per cent NaCl solution was chosen, which is the physiological salt-solution of the pharmacopoeia and most easily available. The tests were carried out in the morning before the experimentees began to work in order to avoid influence from the electrolytic changes caused by work (Siedeck and Zuckerkindl).

In rabbits Aldersberg and Perutz found regional differences as to the disappearance time in the same animals. Consequently the disappearance time was examined in different parts in the same persons. The papules were produced on the inner sides of the legs and the thighs backwards (where we expect to find declivous edema), in the flanks of the wall of the abdomen (considering inflammatory edema occurring at abdominal abscess, and perinephritis), and on the volar side of the forearm, and the extensor side of the brachium. The normal material is composed of 50 men and 50 women, aged 21—45 without cardiac, nephritic, or metabolic diseases in the anamnesis or without clinical signs of such diseases. Nor were any signs of skin diseases to be found.

It would take up too much space to present the values in tabular form, and so I restrict myself to giving average values, and the values that indicate the character of the observation series. The disappearance time varied between 41 and 70 minutes. On the calves of men the arithmetical mean was 53.5 minutes and the standard deviation (σ) = ± 6.7 minutes. In women the corresponding values were 53.7 minutes and ± 6.5 minutes. The values are practically identical and as, moreover, the distributions of the

observations within the series differ but little from each other, I have put together the two series, and the result is an arithmetical mean of 53.6 and a standard deviation (σ) of ± 6.6 . The standard error of the standard deviation, $\epsilon(\sigma) = \pm 0.48$. The average deviation (δ) = 4.9 with standard errors, $\epsilon(\delta) = \pm 0.36$. Within these limits fall 59 per cent of the observations, pointing to a normal distribution of the material. When I made corresponding calculations of the values of the disappearance times for the different parts of the body, I could find no certain difference. It is evident that these examinations do not show any regional difference in normal persons.

The Disappearance Time in Cases of Edema.

A number of cardiac and nephritic cases were examined. The edema being palpable the disappearance time was short. It has not been possible to establish any difference as to disappearance times in these different kinds of illness. In big edema it is often impossible to make any papules, as the fluid injected at once disperses in the tissue. The examiner has a feeling of injecting direct into a system of small cavities filled with fluid.

In cases of cardiac diseases with declivous edema the latter has been mapped out by palpation and intradermal salt solution tests. Within certain parts, where it has been impossible to palpate edema the disappearance time may have been normal or somewhat shortened, in the latter cases owing to the occurrence of latent edema. It has been possible to establish the presence of the latter, or perhaps rather the probability of its existence by the fact that the disappearance time has increased and finally reached normal values, when the patient has recovered, and that *palpable edema* has disappeared at the same time as the disappearance time within these parts has arrived at normal values.

We can get an idea of the limit value of the disappearance time between palpable and not palpable edema (latent edema) by following the disappearance time within regions with palpable edema during its retrogression. It is evident that we get a fairly broad zone for the disappearance time and no sharp limit. In most of these cases the disappearance time of the palpable edema is found to be less than 20 minutes. Sometimes it is impossible, at least with certainty, to palpate edema, when the disappearance time is still between 15 and 20 minutes. I must also point out

the difficulty in palpating the edema of fat persons on spots where there is no firm substratum for the palpating finger. This limit value of the disappearance time may also very well be determined in the legs of persons with varices. (Normal skin is presupposed.) It is fairly easy to bring about a stasis edema through increased transudation, as the venous stasis causes increased capillary pressure, when the legs hang down slack. The edema disappears easily after the removal of the venous stasis, when the legs are raised. In this way we can follow the disappearance time both during the formation and the removal of edema. The disappearance time being observed in this manner, it was found that after having had normal values, it decreased and before it was possible to palpate edema it had fallen to 15—20 minutes.

Intradermal Salt Solution Tests and Mercurial Diuretics.

In their work »Die Quecksilberdiurese» Engel and Epstein alleged *inter alia* a decreased resorption time of an intracutaneous normosal papule as a proof of the extrarenal effect of mercurial diuretics. »Während der Salyrganwirkung wird die intracutan eingespritzte Normosallösung rascher resorbiert als vor derselbe.»— They present figures from 3 cases. In one case of aortitis luetica with edema the disappearance time decreased from 45 to 38 minutes half an hour after intravenous injection of salyrgan. After the same patient had got rid of the edema the time went down from 80 to 36 minutes, conditions otherwise being identical. It is not mentioned if the intradermal salt solution test was made on a part of the body without edema, which was perhaps the case to judge from the long disappearance times. In two other cases, where the presence or absence of edema is not stated, they found a similar decrease of the disappearance time, but not so marked.

The author has made another examination of this in persons suffering from cardiac diseases with edema. Considering the risks of serious renal injuries — degeneration of tubuli contorti (Griff) — experiments have not been made on persons without certain depots of fluid. The excretion of mercurial diuretics proceeds or the whole independently of the simultaneous elimination of water and if the diuresis should not increase, the concentration could reach such high values that tubuli contorti were injured (K. O. Møller).

First the extension of edema was mapped out by palpation and

intradermal salt solution tests. Then the presence or absence of latent edema was determined. The patients had beforehand been treated with 6 g ammonium chloride a day for two days. After an experimental dose of 0.05 g, showing increase of the diuresis; 0.20 g salyrgan was given intravenously. Before the salyrgan injection was given the disappearance time was determined in parts with palpable edema, where they were still latent, i. e. not palpable, and in parts without edema. The disappearance time was then followed with intervals of 15 minutes during the first two hours, the first reading off taking place 15 minutes after the salyrgan injection. It was then determined 6 hours and 24 hours after the injection. In the 9 patients so examined no positive decrease of the disappearance time could be found, either in edematous or in non-edematous regions or in regions with latent edema. The disappearance time showed a variation of 5 to 7 minutes in regions without edema and of 2 to 3 minutes in edematous regions, that is to say, only the standard error inherent in the method. It is evident that the intradermal salt solution test is too insensible or too uncertain.

These investigations have to a certain extent been carried out parallel with those made by Frantzell as to the radiographs of edema, accomplished in the radiographic department of this hospital. In the cases investigated both by means of radiographs with soft tissue technique and intradermal salt solution tests there was found good agreement between the methods as to the absence or presence of edema.

Subsequently I have made some experiments in order to find out, how long it was possible by radiographs to see the changes in the skin caused by the injected salt solution and, on the other hand, how long it was possible to palpate the papule. Papules produced by the method mentioned above were made in the cutis and their disappearance was observed by means of palpation and radiographic films according to Frantzell's soft tissue technique. In contradistinction to him I have not had the opportunity of using the fine grain intensifying screens »Rubray». The pictures have therefore been exposed without intensifying screens on Gevaert's Osray-film with the times of exposure corrected for this film (film-focal distance 150 cm, 150 kV — 300Ma — 1.5 sec.).

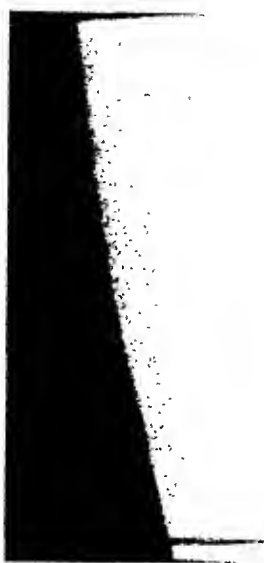


Fig. 1. The normal cutis and subcutis.

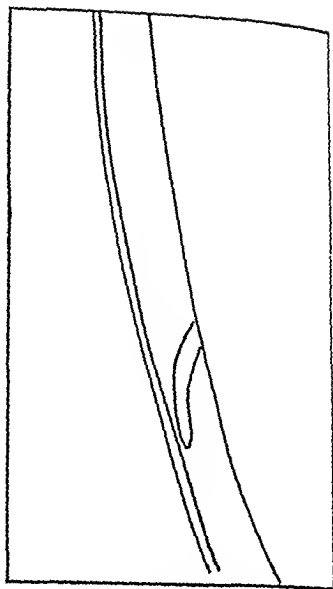


Diagram to fig. 1.

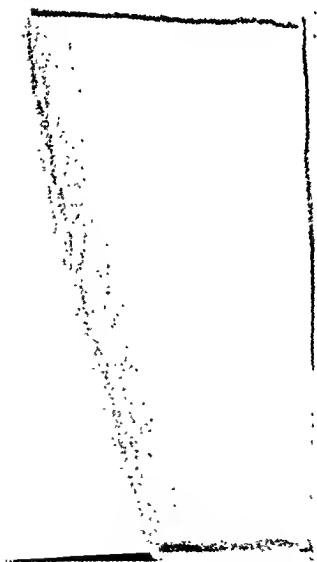


Fig. 2. The papule not palpable. Still slight broadening and denseness of the cutis line. Streaked markings below in the subcutis.

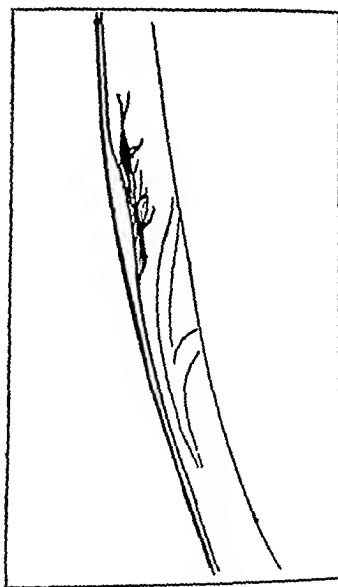


Diagram to fig. 2.

First I wish to call attention to the radiographic symptoms of edema that Frantzell has indicated:

1. A broadening of the subcutaneous fat layer.
2. Abnormal, partly net-formed, markings in this layer.
3. A broadening and an increased denseness of the cutis line.

On radiographs it is possible to see the normal cutis and subcutis, fig. 1. When the papule has been made, a broadening and an increased denseness of the cutis line can be noticed and also streaked markings in the subcutis below. When the papule has ceased to be palpable (in this case after 42 minutes), it is still possible to see the slight local broadening of the cutis line and the streaked markings below, fig. 2. After 60 minutes faintly increased streaked markings can be seen below the former papule. On this spot the cutis line then had the same breadth and denseness as in the environment.

The results of several other experiments are analogous. It is evident that the local edema that the papule constitutes, can more easily and longer be observed by suitable radiographic technique than by palpation.

Summary.

1. The disappearance time found in a normal material consisting of 50 men and 50 women, aged 21—45, varied between 41 and 70 minutes, the arithmetical mean being 53.5 ± 6.5 minutes.
2. In normal skin the standard error of the method is 4—5 minutes. If the disappearance time is shorter (edema) the corresponding error is about 3 minutes.
3. 0.8, 0.85 and 0.9 per cent NaCl solution can be used as well as Ringer's solution.
4. Impalpable (latent) edema can be indicated and followed as well as palpable edema in its formation and disappearance.
5. If the presence of latent edema is to be established the greatest certainty is reached by simultaneous use of the intradermal salt solution test and radiographic examination with a special technique.

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Partial A-V Block and Duodenal Ulcer.

Report of Two Cases.

By

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The question of the origin of peptic ulcer has been under discussion for over 100 years and is still not settled. Many theories have been brought forward and have to some extent been a mirror image of the, from time to time, predominant theories of pathology in general. Recent surveys have been given by Laurell (15), Ask-Upmark (3), Brun (5) and others in the Scandinavian literature. More and more have neurological and hormonal points of view been stressed, and by some investigators peptic ulcer has been regarded as almost a psychiatric disease. The authors do not want to enter the discussion but they think it correct to emphasize that the neurogenic point of view has been proved both in experimental and in clinical work during recent years, although it cannot be said that this pathogenesis is the only one. Rokitsky seems to have been the first to put forward the theory of the neurogenic origin of the peptic ulcer, and the observations by Harvey Cushing on patients operated on for brain tumours gave certain evidence to this theory. It was thought by Cushing that the peptic ulcer might be due to some disorder of parasympathetic centers in the hypothalamus and that the impulses were transmitted through the vagus nerve to the gastric mucosa. The theory was to a certain degree confirmed by others, who were able to produce gastric ulcerations by injection of pilocarpine into the third ventricle or by continuous stimulation of the vagus nerve. The classical experiments of

Pavlov regarding the secretion of the gastric juice and later studies by Wolf and Wolff (28) have shown the strong influence of nervous tone on the gastric secretion. In his stimulating survey of the adaptation syndrome Hans Selye (22) has shown the effect of shock conditions on the gastric mucosa and also stressed the evidence that adrenalectomized animals, where the hormonal counterbalance of the parasympathetic system is decreased, show more severe damage than do other animals. It seems therefore as if there were a large bulk of evidence showing that the connection between the parasympathetic nervous system and the peptic ulcer is rather close. It is also well known that this conclusion has originated a new operative approach to peptic ulcer disease, namely the resection of the vagus nerves (7, 8, 20, 23, 29), and the reports hitherto encountered have been in many cases favourable both with regard to its influence upon the secretory function of the gastric mucosa and to the relief of the subjective sensations of the patients.

Peptic ulcer is predominantly a disease of the male. Very little has been known about peptic ulcer in children but it has been said that the frequency of such lesions is small. A recent summary of the published cases together with some new one has been given by Forssell (11, 12). It is interesting to find that of the 7 cases published by him 5 are between 12 and 14 year old, *i. e.* an age at which vegetative disturbances are very common. Winkelstein (27) has also published a number of cases with peptic ulcer in adolescence, which he believes to be connected with dysfunction of the anterior pituitary. On the other hand he admits that psychologic or emotional disturbances could also have been the aetiology.

Many organs are influenced by the vagus nerve and the heart is also commonly affected. The vagus action on the heart is characterized by such features as bradycardia, A-V-block, and changes in the ECG with regard to the shape of the S-T segment and the T wave. The effect on the shape of the ECG has been studied, among others by Ask-Upmark (2), Nordenfelt (21) and Lind (18). A survey of the action of the vagus nerve together with other mechanisms in the production of A-V block and Adams-Stokes syndrome has been given by Biörck (4). Wei and Ferris (26) have demonstrated in a case of diverticulum of the oesophagus that distension of the diverticulum promptly induced auriculoventricular dissociation of the heart and syncope.

and this mechanism was shown to be entirely dependent on the vagus nerve. Marcus, Sahlgren and Bjerlöv (19) reported a case with a tumour metastasis in the cerebral nucleus of the vagus nerve, which elicited attacks of Adams-Stokes syndrome. Robert C. Levy (17) has shown, in a 14 years old boy, a persistent A-V block, which was abolished by atropine. This boy was reported to show no other evidence of vagotonia. Holmes and Weill Jr. (13) have reported three cases with prolongation of the P-R interval in the supine position, whereas a normal P-R interval was attained in the erect position. In two of the cases atropine restored the P-R interval to normal limits, a fact which did not completely happen in the third case. In the first two cases exercise also brought the P-R interval back within normal limits. All cases were healthy young males without any evidence of disease. The authors also relate Levy's and one other certain case from the literature, a 15 years old child where the same alteration in the P-R interval was observed with change of position. The effect of atropine on the P-R interval is regarded as a proof of the vagal origin of the observed abnormalities. (This may perhop not be quite correct.)

Studies on the electrocardiographical findings in gastroduodenal ulcer and associated conditions have been reported by several investigators (6, 9, 14). Bradycardia, elevated S-T segments and large T waves are considered significant of the "ulcer ECG". Some authors, however, point to pictures simulating coronary insufficiency, which is more or less the opposite. It seems, as if the electrocardiographic coronary insufficiency were related to an *acute* stage of the disease, probably with cardiac reflexes elicited from visceral pain, whereas the typical "ulcer ECG" is an expression of a constitutional disorder. Although statistically some prolongation of the P-R interval within the normal limits has been observed in cases with peptic ulcer, more marked changes in the auriculo-ventricular conduction are rarely mentioned. In a large series of 200 cases of peptic ulcer Waider (24) reports three cases with, respectively, prolonged P-R (0.23 sec.), Wenckebach periods and A-V rhythm, all of which were abolished by administration of atropine. Also Lehman (16) had one case, where prostigmin induced Wenckebach periods. We have also seen a man, 49 years of age, with duodenal ulcer, whose ECG showed varying degrees of A-V block, complete heart block and Wenckebach periods. Because of his age and his admittance of a luetic

infection at the age of 27, we have not felt it correct to include him in the present report. Apart from the conduction disturbances there was however no evidence of heart disease per se (auscultation, roentgenological heart volume and blood pressure revealing no other abnormality). The Wassermann test was negative.

We have recently seen two cases, both of which were originally brought to the hospital on account of peptic ulcer and in whom routine ECG disclosed changes in the auriculoventricular conduction time, which as far as we can see, must be vagal of origin. Although one must always bear in mind the possibility of the patients having two separate diseases it seems plausible that the common denominator in these cases with their two diseases was the vagus nerve or, perhaps, the parasympathetic nervous system.

Case 1. A boy 14 years old.

Two uncles had peptic ulcer. Since the age of six the patient had complained of pain in his abdomen. Appendectomy revealed no inflammation of the appendix. The boy has always been regarded as neurotic child, and since the age of 10 he has complained of vertigo in the standing position. He was seen by a psychiatrist because of his neurotic condition and his repeated complaints of abdominal pain and was referred to the psychiatric ward of the hospital. The abdominal pain was located in the middle of the epigastrium. He had no vomiting and no "heart burn". At the psychiatric ward an X-ray of the stomach was taken and a typical duodenal ulcer and signs of gastritis were found. The ventricular acidity was found to be at the upper limit of the normal. There were no other pathological findings on ordinary laboratory investigations. He was put on the ordinary peptic ulcer diet and received some phenobarbitone and atropine. After 5 weeks he was discharged from the hospital, subjectively improved. At that time the ulcer was healed, but some gastritis was still seen on the X-ray. Two months later the boy was seen by one of us (G. B.) because of his vertigo. This had been so marked that he had remained away from school. When walking in the street he suddenly experienced nausea and vertigo and had to go home and go to bed. Some of the sensations in this connection had a slightly psychopathological color. *i. e.* he felt that his hands and feet decreased in size and disappeared.

The physical examination revealed a tall asthenic boy of normal intelligence and without any signs of cardiac decompensation. The lungs and abdomen were normal, and nothing pathological was found neurologically. The Wassermann test was negative, and usual laboratory findings were entirely normal.

The heart revealed nothing abnormal on auscultation. The X-ray showed an absolute heart volume of 400 ccs. according to Kahlstedt corresponding to 200 ccs. per sq. m. body surface, which is a very high value. Blood pressure: 140/100, after 5 minutes standing: 120/90. Blood pressure in the legs: left: 180/110, right: 170/90. Oscillogram

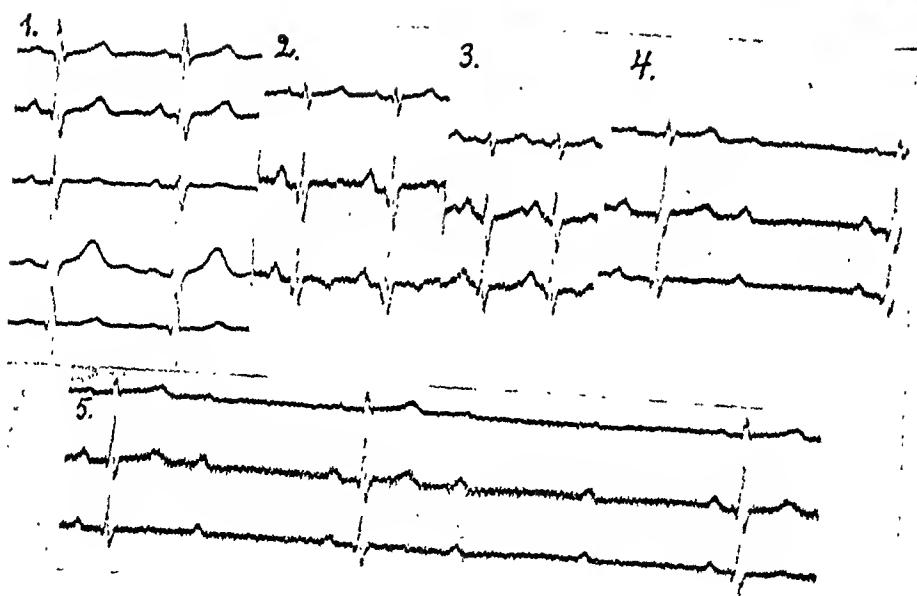
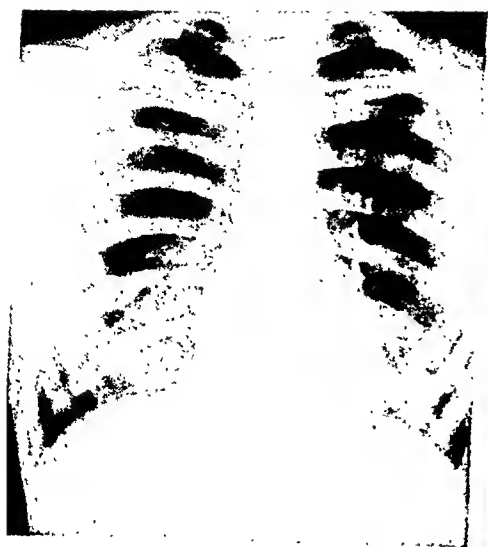


Fig. I. Case I.

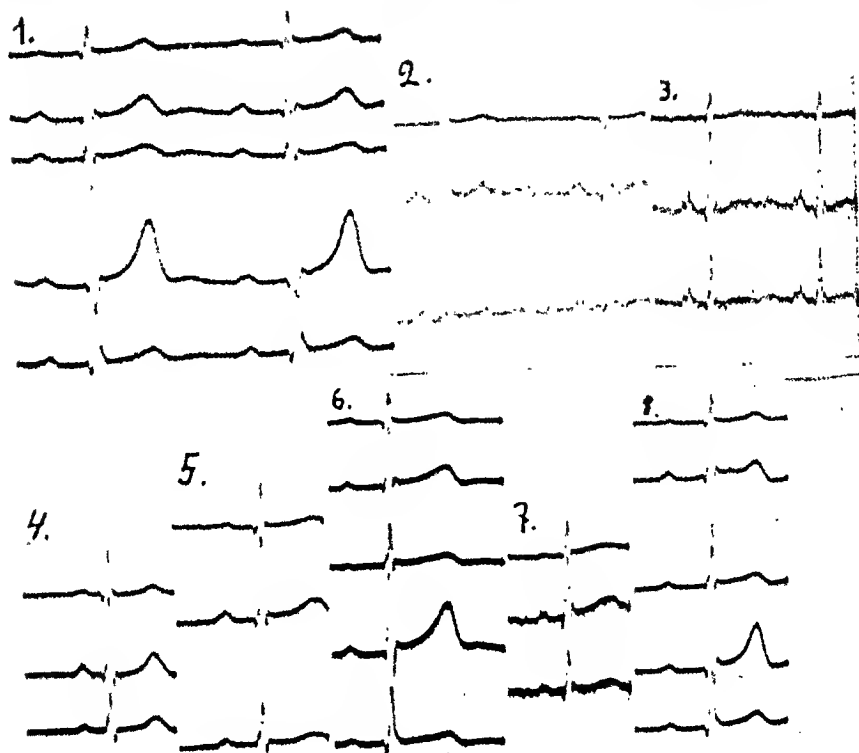
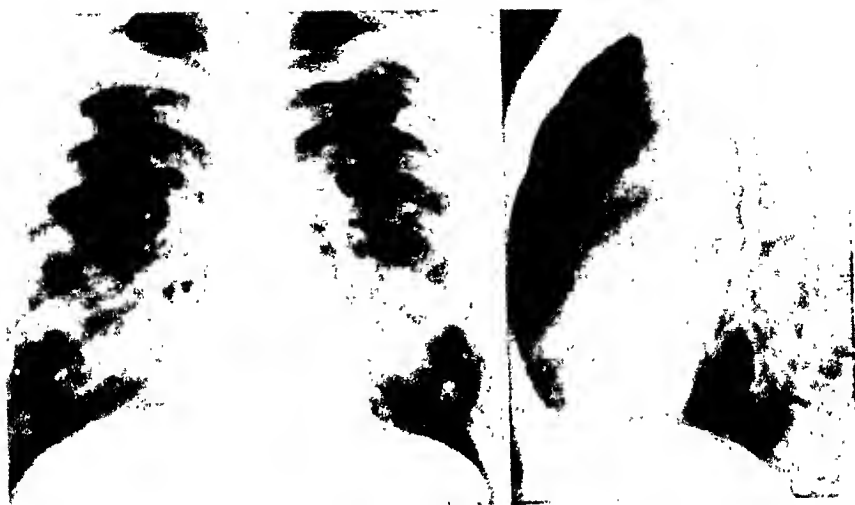


Fig. 11. Case 2.

according to Ejrup: normal pulsations resting, and after work. Eye- and ear specialist consultations revealed nothing abnormal and gave no explanation for the vertigo. Functional test according to Nylin showed normal oxygen consumption even after heavy work. BMR + 8%.

Electrocardiograms: (See Fig. I.)

a) Resting: Heart rate 92 per minute. P-R interval 0.13 sec. QRS time 0.09—0.10 sec. Normal electrical axis. P II and P III slightly accentuated. TI, TII and T in the chest leads positive, T III negative. Nothing abnormal in the S-T segments. (Fig. I: 1.)

b) Standing: Very pronounced increase of heart rate from 75 per minute to 170 per minute in the first minute. P waves very marked in II and III. T III inverted and T II diphasic. The changes were regarded as signifying an orthostatic reaction. (Fig. I: 2.)

c) After deep inspiration: There was an increase in heart rate. PII and PIII increased, whereas TII was decreased and TIII slightly inverted.

d) Carotid sinus pressure: The sinus arrhythmia is somewhat more marked, otherwise no definite change.

e) After moderate exercise: There was a slight decrease in the P-R interval, TI, TII and TIII were somewhat increased, otherwise no definite change.

f) Hypoxaemia test: The test was interrupted after 5 minutes because of a feeling of discomfort in the chest and some vertigo. There was no change whatsoever in the S-T segments or T waves: A negative hypoxaemia test. A second hypoxaemia test was performed during 10 minutes. There were no pathological changes in the ECG.

g) After administration of $\frac{1}{2}$ mgm. atropine subcutaneously: there was a decrease in the P-R interval from 0.11 to 0.11—0.12 sec. with approximately the same heart rate. Otherwise no change. The orthostatic changes provoked by the standing position were not definitely altered although the negative TIII in the standing position before atropine was slightly more marked than after atropine.

h) After administration of $\frac{1}{2}$ mgm. ergotamine tartrate ("Gynergen") subcutaneously: 20—40 minutes after the administration of ergotamine the heart rate was decreased from 87 per minute to 55 per minute. The P-R intervals were 0.14—0.15 sec. in both ECGs. The ECG in the same orthostatic picture as before. The ECG in the standing position 20 minutes after the administration of ergotamine was of great interest, however. The orthostatic changes were almost totally prevented (Fig. I: 3) and instead there appeared another unsuspected abnormality namely different degrees of A-V block. Whereas the P-R interval in the standing position before ergotamine was 0.15 sec. it was increased to 0.18 à 0.20 sec. in the beginning of the ECG in the standing position (Fig. I: 4) and then followed by a partial blocking with dropped beats in the ratio 2: 1 and in the latter part of the curve (Fig. I: 5) alternating 2: 1 and 3: 1. This shows very well that the abolition, by ergotamine, of the sympathetic activity which counteracts the vagal overactivity, results in a marked vagotonia. It also proves that the sympatheticotonia

present before the administration of ergotamine was responsible for the orthostatic reactions in the standing position.

Case 2. Engineer, 26 years old.

One brother has had peptic ulcer. The patient smokes 10—15 cigarettes daily but takes no alcohol. Appendectomy at the age of 12, otherwise healthy until one month ago, when he experienced gastric pain, that ceased 10 minutes after meals. An X-ray was taken and showed a duodenal ulcer. The patient was referred to hospital for dietary treatment. He has had no symptoms from his heart and no history of rheumatic infection. At hospital he was found to have a moderate hyperacidity. Otherwise all laboratory findings were negative.

The physical examination showed a man of asthenic stature. Nothing abnormal was found in the alimentary tract or on neurological examination. The auscultatory findings from the heart were normal and the blood pressure on admission was found to be 150/85. The Roentgenological heart volume was 670 ccs., i. e. 340 ccs. per sq. m. body surface.

Electrocardiograms: (See Fig. II.)

a) Resting: Sinus rhythm 57 per minute. P-Q interval 0.27—0.28 sec. QRS time 0.03 sec. Normal electrical axis. Slight elevation of S-T segment in all leads. All T waves positive. ECG diagnosis: A-V block I and possibly vagotonia. (Fig. II: 1.)

b) Standing: Slight increase in heart rate from 55 per minute to 75 per minute. The P-R interval decreases from 0.27 to 0.20 sec. and is after 10 minutes standing 0.17 sec. with a heart rate of 85 per minute. The T waves have all decreased in amplitude but there is no orthostatic reaction. (Fig. II: 2, 3.)

c) After deep inspiration: Sinus rhythm 67 per minute. The P-R interval has decreased from 0.27 sec. at rest to 0.24 sec. Otherwise no changes.

d) Carotid sinus pressure: Sinus rhythm 55 per minute. P-R interval 0.27 sec.

a) After moderate exercise (ECGs taken in the supine position): Whereas the P-R interval at rest was 0.24—0.25 sec. at a heart rate of 55 per minute the P-R interval after exercise (Fig. II: 4) is 0.15 sec. at a heart rate of 60 per minute immediately after work and 0.21—0.22 sec. 3 minutes after work (Fig. II: 5). There are no marked changes in the T waves, but the S-T segments are elevated in all leads at rest and at about normal level immediately after exercise. After 3 minutes the tendency to elevation appears again.

f) Hypoxaemia test: Negative hypoxaemia test after 10 minutes. P-R interval before the test 0.29 sec. and after the test it remains 0.29 sec.

g) After administration of $\frac{1}{2}$ mgm atrophine sulphate subcutaneously; 20 minutes after the administration of atropine there is a sinus rhythm of 52 per minute. The P-R interval is the same as at rest, 0.27—0.28 sec. In the standing position the heart rate is 67 per minute and the P-R interval decreases to about 0.16 sec. No orthostatic reaction. Thirty minutes after the administration of atropine the heart rate

50 per minute and the P-R interval 0.24 sec. (Fig. II: 6.) In the standing position there is a sinus rhythm of 75 per minute and a P-R interval of 0.11—0.13 sec. (Fig. II: 7). No orthostatic reaction. (h) After administration of $\frac{1}{2}$ mgm. ergotamine tartrate ("Gynergen") simultaneously: 20 minutes after the administration of ergotamine the heart rate has decreased from 55 to 50 per minute and the P-R interval increased from 0.27 to 0.28—0.29 sec. (Fig. II: 8). There are no other changes in the ECG. The P-R interval in the standing position is 0.19 sec. Thirtyfive minutes after the injection there is a decrease of P-R interval to 0.25—0.27 sec. and in the standing position the P-R interval is about 0.21—0.22 sec. Fifty minutes after the injection the respective figures are 0.29 and 0.17 sec.

In this case there is obviously a prolonged A-V conduction time, which is mainly provoked by the supine position, whereas the conduction time in the standing position is normal. The amount of prolongation of the A-V conduction time is variable within the limits of 0.29—0.15 sec. (resting; immediately after exercise). There is a day-to-day change from 0.27—0.29 sec. Atropine decreases the P-R interval somewhat, both in the supine and in the standing position, although the value in the supine position is not brought back within normal limits. The great variability in A-V conduction time must however be regarded as evidence of the "functional" character of the abnormality and there are few other explanations than changes in vagal tonus. The normalization of the ECG in the standing position is in some way the opposite of the pathological changes seen in orthostatic reactions of sympathetotonic origin.

Discussion.

Both cases showed the following features. They are young asthenic males with duodenal ulcers, verified by X-ray. Their ECGs show, either in the resting state, (case 2), or after blocking of the sympathetic with ergotamine, (case 1), signs of increased vagal tone. In case 1 there is also seen a very pronounced orthostatic reaction, which is probably sympathetic in origin, as it could be prevented by ergotamine. In this latter case one will therefore probably have to speak about a vegetative instability affecting both the vagus and the sympathetic. The increased vagal tonus is in some respects counterbalanced by the increased sympathetic tonus. The boy was treated with bellergal, a compound of belladonna, ergotamine and phenobarbitone, and this medication has to a large extent relieved him of his vertigo.

We are inclined to think that the duodenal ulcer and the disorder of the auriculoventricular conduction are due to one and the same mechanism, namely that of an increased vagal tone or possibly some disturbance of the parasympathetic cerebral centers.

We also think that the occurrence of peptic ulcer in adolescence and young adults should draw the attention to the possibility of such a neurogenic origin of the disease and it might be that electrocardiographical studies of the present kind, with functional and pharmacological tests will reveal also corresponding disturbances of the electrical activity of the heart. In cases of such a type, treatment apparently should be directed against the primary cause of the disease and not only against its local manifestations.

Summary.

After a brief review concerning the theories of the origin of peptic ulcer, especially the theory of its neurogenic origin, and also of the physiological background of functional auriculo-ventricular conduction defects the authors report two cases of duodenal ulcer with disturbances of the auriculoventricular conduction time. In the first case, a boy 14 years of age, a hidden vagal over-activity was found. This revealed itself when the sympathetic was blocked by means of ergotamine. An increased sympathicotonia was also found, which manifested itself by strong orthostatic reactions. In the second case, a man 26 years of age, there was, in the supine position, an A-V block I with a prolonged conduction time of 0.27—0.28 sec., which however completely disappeared in the standing position. It is believed, that the cause of both the duodenal ulcer and the conduction abnormalities in question is an increased vagal or parasympathetic tonus, and it is recommended to submit cases of peptic ulcer in children and young adults to a thorough electrocardiographical examination in order to discover, whether the peptic lesion is a local disease or an expression of a general, increased action of the parasympathetic nervous system.

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Are the Basophilic Leucocytes "Heparinocytes"?

Part I.

By

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Introduction.

In 1937 Jorpes, Holmgren and Wilander stated that heparin, the anticoagulant of the animal body, is formed in Ehrlich's mast cells which occur in particular abundance in the tissue around the smallest blood vessels. The discovery was made by the mentioned authors on account of the capacity of heparin to stain metachromatically, a tinctorial quality which already Ehrlich had ascribed just to the granules of the mast cells. The writers were supported in their theory that heparin originates from the mast cells by being able to state a parallelism between the number of mast cells in the tissue and its content of ester sulphuric acids which form an important part of heparin. Jorpes, Holmgren and Wilander's discovery concerned Ehrlich's mast cells which are tissue mast cells. A question arose regarding the basophilic leucocytes, the granules of which are also metachromatically stainable. Are they, too, heparin producers? This idea occurred to R. Ehrström as he gave them the name »heparinocytes». A priori the thought seems justified; metachromasia is common to heparin as well as to the granules of the mast cells and of the basophilic leucocytes. But, on the other hand, different opinions have been heard regarding their identity. Earlier no difference was made between mast cells of the tissues and those of the blood, to-day hematologists, as a rule, have adopted the position that, morphogenetically considered, two unrelated types of mast cells exist in adult mammals. In the

¹ Lady Tata Memorial scholar.

first hand they are dissimilar in configuration. The shape of the basophilic tissue cells may vary greatly and the nucleus is small in comparison with the cell body. The basophilic leucocytes are round and have a large nucleus and but little plasma. The granules are large and if the cell wanders into the tissue it retains its appearance.¹ There is a possibility, however, that both these kinds of cells are identical with regard to function. N. A. Michels, namely, stated in mammals an inverse numerical relationship in the cells in question. In fish, the dog, cat, rat, and mouse the basophilic leucocytes are sparse or lacking, but Ehrlich's mast cells occur in abundance. In the rabbit the condition is reversed.

The question whether the basophilic leucocytes, primarily in man, contain heparin or not is of theoretical interest. A certain clarity may perhaps be obtained by study of clinical series. The case is that in chronic myeloid leucemia, basophilic leucocytes may sometimes appear in great abundance. If the basophilic leucocytes contain heparin it might be supposed that it might cause a tendency towards increased bleeding. As known, a hemorrhagic diathesis occurs in some cases of leucemia, especially in the acute type of the disease. As a thrombocytopenia is often present simultaneously there is a probability that this disorder plays an important part in the origination of the hemorrhage. It is not known, however, whether the basophilic leucocyte count is influential in this connection. The heparin does not change the bleeding time but a prolongation of the coagulation time, brought about by the heparin, might cause manifest hemorrhages although the number of platelets is not reduced to any extent. In hemophilia, for instance, the greatly delayed coagulation time is the fundamental abnormality, as known. If there were a certain parallelism between basophilia and bleeding tendency, it might be a sign of the basophilic leucocytes containing heparin.

Results.

For the purpose of studying whether basophilia predisposes to hemorrhage I have surveyed a series comprising 88 cases of myeloid leucemia. The patients were admitted to the Medical Clinic of Maria Hospital (Head: Professor Fredrik Saltzman), to the First

¹ In addition to this the blood mast cells show positive indophenolblue synthesis and peroxidase reactions while on the other hand the tissue mast cells give a negative reaction (Naegeli).

Medical Clinic (Head: Professor W. Kerppola) or to the Second Medical Clinic during the years 1930—1947. A series of this kind is naturally deficient to a certain extent, especially with a view to finding an answer to the problem in question. Information on platelet count, bleeding and coagulation time is often lacking, but as data are given regarding the blood picture, comprising differential counting of leucocytes, and detailed case reports with notes on hemorrhages in past history and present state, I have, however, found the series satisfactory. At Maria Hospital the number of platelets were calculated approximatively in each case, and, as this was done by a routined laboratory assistant a certain value may be attached to the results. For brevity the series are given in tabular form and only essentials — with regard to blood picture and clinical picture — of importance for the investigation are included.

Cases 1—31 were treated at Maria Hospital, cases 32—50 at the First Medical Clinic, and cases 51—88 at the Second Medical Clinic. In 12 cases (Nos. 1, 3, 5, 6, 20, 22, 30, 43, 44, 75, 83) the diagnosis was acute myeloid leucemia and in the remaining cases chronic myeloid leucemia. Cases of lymphatic leucemia have naturally not been included as basophilia does not occur in this disease. The basophilic leucocytes are given in percentage of the leucocyte count and in total number per cmm. Surveying the series from Maria Hospital we find that in 8 cases the percentage for the basophils is above 8 per cent (Nos 7, 10, 13, 16, 17, 21, 23, 28), in the last-mentioned case (No. 28) the figure is as high as 45 per cent. On account of the low leucocyte count the total number of basophils is low in this case similarly as in the analogous cases Nos 21 and 23. High total basophil values were found in cases 16, 10 and 17 and to some extent also in cases Nos. 12 and 2. Subcutaneous bleeding occurred only in case 2. There were no signs of hemorrhagic diathesis in the other cases, despite a pronounced basophilia.

According to the hospital reports the thrombocyte count was reduced in case 2, and in the remaining chronic cases either normal or abundant. Investigating when and in what connection hemorrhages occur we find in the first hand, that subcutaneous and submucous hemorrhages were present in all acute cases, excepting one (No. 5). In all the acute cases the thrombocytes were distinctly decreased; the basophils, again, occurred sparingly or were totally lacking. Three (Nos 4, 19, 24) of the chronic cases showed a certain

BASOPHILIC LEUCOCYTES.

Table 1.

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Case	Leucocyte count	Basophils		Blood platelets	Hemorrhages	
		%	total		in history	in present state
1	25,600	—	—	diminished	submucous	—
2	527,000	1.8	9490	»	—	cerebral
3	19,700	0.4	79	»	cutaneous	cutaneous
4	23,400	5.0	1170	»	»	» + sub-
5	8,100	—	—	»	—	muc.
6	58,800	0.2	118	»	—	cutaneous
7	56,400	8.8	4963	abundant	cutaneous	—
8	5,300	0.4	2150,000	—	nasal + genital	submucous
9	336,800	1.7	5726	normal	—	—
10	202,000	9.75	19695	268,000	—	cutaneous + sub-
11	256,000	—	—	abundant	—	muc.
12	382,000	3.5	13370	»	submucous	—
13	13,700	10	1370	»	—	—
14	138,200	5	6910	»	—	—
15	34,800	1	348	normal	—	—
16	216,800	14.5	31436	»	—	—
17	114,800	16	18368	abundant	—	—
18	129,200	0.75	970	normal	—	—
19	97,800	2	1956	abundant	—	—
20	7,500	—	31,600	—	—	—
21	22,900	25	5725	abundant	cutan. + submuc.	—
22	235,000	—	117,000	—	—	—
23	8,400	—	382	abundant	cutaneous	cutan. + intestin.
24	6,200	10.5	—	sparse	—	—
25	345,000	2.25	7763	normal	cutaneous	cutan. + submuc.
26	85,000	1	850	»	—	—
27	276,000	2.4	6624	sparse	—	—
28	9,300	45	4185	abundant	—	—
29	13,500	6	810	normal	—	—
30	1,328	—	—	sparse	—	—
31	9,300	7.5	688	normal	—	—
32	104,600	2.5	2615	—	—	—
33	104,000	1	1040	—	—	—
34	353,000	4	14120	200,000	—	—
35	450,000	1	4500	—	—	—
36	21,600	—	—	190,000	submucous	—
37	125,000	—	—	—	—	—
38	45,000	—	—	—	—	—
39	143,000	2	—	—	—	—
40	13,300	1.5	2860	—	—	—
41	14,900	6	200	—	—	—
42	280,600	11.5	894	—	—	—
43	315,000	2	32269	163,000	—	—
44	18,900	3.5	6300	52,500	—	—
45	70,800	—	—	75,000	submucous	—
46	159,000	14.5	2478	—	—	—
47	205,000	3.5	23055	—	—	—
48	760,000	3	7175	—	—	—
49	58,000	1.5	2280	—	—	—
50	125,000	8	870	155,000	—	—
51	387,000	6	10000	250,000	—	—
52	204,000	3.4	23220	—	—	—
			6936	—	—	—

Table 1 (cont.).

Case	Leucocyte count	Basophils		Blood platelets	Hemorrhages	
		%	total		in history	in present state
53	238,000	1.8	4284	29,400	—	—
54	774,000	0.6	4644		cutan.+submuc.	cutaneous
55	70,400	7.2	5069		—	—
56	40,200	4.2	1688		—	—
57	217,000	0.2	434		—	—
58	11,900	3.5	417		—	—
59	337,000	7.3	24601		—	—
60	192,000	5.5	10560		cutan.+genital	cutan. + genital + submuc.
61	247,000	8	19760		—	—
62	23,400	—	—		—	—
63	562,000	0.5	2810	675,000	—	—
64	409,000	—	—		—	—
65	37,000	1	370		—	—
66	29,400	8.5	2499		—	—
67	35,600	0.5	178		—	—
68	91,400	0.5	457		—	—
69	140,000	2	2800		—	—
70	172,400	3	5172		—	—
71	63,700	3.5	2230		—	—
72	65,500	—	—		—	—
73	434,000	2	8680	50,000	—	—
74	198,000	1	1980		—	—
75	28,500	0.5	143		hematuria	hematuria+cutan
76	310,000	—	—		»	—
77	48,000	8	3840		—	—
78	10,450	1.5	157		—	—
79	12,800	—	—		—	—
80	317,000	—	—		submucous	submucous
81	128,000	1.5	1920		submucous	submucous
82	17,650	—	—		—	—
83	1,650	—	—	27,000	—	—
84	442,000	—	—		—	submucous
85	12,000	—	—	120,000	—	—
86	272,000	—	—		—	—
87	316,000	0.5	1580	30,000	submucous	submucous
88	244,000	1	2440		»	—

tendency towards bleeding. The platelet count was diminished only in case 24. In this case the basophils were totally absent, in the two other cases they were present in moderate amounts. Coagulation time was found to be normal in the solitary cases in which it was determined. Bleeding time was distinctly prolonged in case 20 which was one of the acute cases with a distinct thrombocytopenia.

Among the cases admitted to the First Medical Clinic two were of the acute type (Nos 43 and 44) with thrombocytopenia hemorrhages and low basophil values. In three cases (Nos 42, 46, 34)

the number of basophils was high. In all three cases there were slight hemorrhages, but there was an increased tendency towards bleeding also in three other cases (Nos 36, 45, 49) with low basophil values. In two of these (Nos 36 and 49) the platelet count was somewhat decreased. In the series from the Second Medical Clinic there was a high-grade basophilia in three cases (Nos 51, 59, 61) without hemorrhagic diathesis being present. In case 60 the number of basophil cells was high and hemorrhages occurred, but the prolonged bleeding time and the low platelet count revealed the cause of the hemorrhages. In one acute case (No 75) and in three other cases (Nos 79, 80, 85) there was a hemorrhagic diathesis and low values for basophils and thrombocytes.

Discussion.

The series from the three clinics seem to point in the same direction. The acute cases of leucemia are characterized, as already known, by strong hemorrhagic diathesis and low thrombocyte counts. Basophils were totally lacking or appeared very sparingly in the acute cases. In the chronic cases with strongly pronounced basophilia there was no evident tendency towards bleeding excepting in connection with a low platelet count. In chronic cases lacking information regarding the thrombocytes there were equally often slight hemorrhages in patients with low basophil values as in those with high counts. Basophilia does evidently not predispose bleeding. It is however impossible to determine on the basis of a clinical material, whether this is due to the metachromatic substance contained in the granules of the basophil leucocytes not being identical with that in the tissue mast cells. In diseases such as leucemia, in which severe disturbances in the blood and the blood forming organs are present it may easily happen that for instance the metachromatic substance has lost qualities which it might possess in normal conditions. Furthermore, the thrombocytes seem to play an overpowering part in the coagulation of the blood, causing all other factors to take a secondary place. With the aid of laboratory methods some clarity might be found regarding the question whether the basophil leucocytes contain heparin or not. My intention is to continue in this direction and to investigate whether a substance which in vitro tests shows the effect of heparin may be obtained from leucocytes in which the basophils dominate.

Summary.

1. Cases of acute myeloid leucemia with low platelet counts and severe hemorrhagic diathesis are often combined with a low number of basophils.

2. Cases of chronic myeloid leucemia with pronounced basophilia do not show greater tendencies towards hemorrhages than do cases without basophilia.

3. A clinical material will not give a reply to the question whether the basophilic leucocytes contain heparin or not; the problem may possibly be clarified by endeavouring to state, in vitro tests, whether a protein-free extract of basophilic leucocytes has the effect of heparin.

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The Efficacy of the so called Anti-Histaminic Drugs in the Paraphylactic (Anaphylactic) Shock does not prove its Histaminic Origine.

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According to the running opinion, the anaphylactic shock, which we called paraphylactic, is elicited by histamine. We have shown¹ that it is provoked by acetylcholine and that histamine is liberated only in second order and especially when we have a state which we called *incomplete immunity*. We give here our conception concerning the formation of antibodies and paraphylaxis (anaphylaxis).

According to our theory, the antigen, when introduced into the organism, liberates, in contact with the cells, the ACh, which stimulates production of globulines; these later ones, in contact with the antigen, form the antibodies. The concentration of tissular precholine (acetylcholinic complex) increases in animals treated with an antigen, and, at least in the cells, remains connected with the antibody.

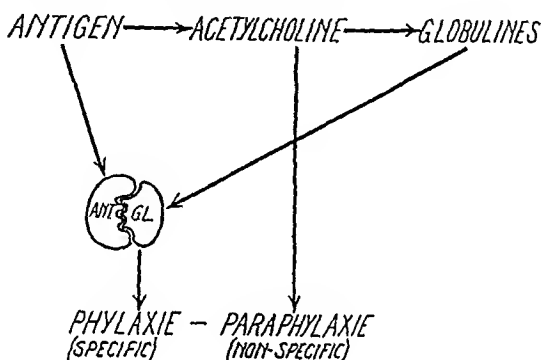
This straight connection between antibody and precholine is named provisionally by us *antibody-choline*. By this term we design

¹ D. Danielopolu: Pathogénie de l'asthme. Archives médico-chirurgicales de l'app. resp. 1931, Congrès de l'asthme de Mont Dore 1932, Deutsche med. Woch. 1943, Acta Medica Scand. 1944, Paraphylaxie G. Doin, Paris 1943, Phylaxie, Paraphylaxie et maladie spécifique, Masson et Cie, Paris 1946.

the connection which exists between the antibody and choline in the cells.

The antibody elicits immunity and the hyperconcentration of choline calls forth paraphylaxis, which is named currently anaphylaxis. Phylaxis (immunity) is specific, but paraphylaxis is not.

The antibodies are all immunising. There is no such thing as anaphylactising antibodies. The antigene elicits but immunity, and sensitising does not exist at all. The thing named so, is merely a tissular hyperconcentration in precholine.



When the same antigen has been introduced into the organism, the antigen together with the antibody and alexine, form the phylactic complex AAA and choline goes out as active ACh and calls forth the paraphylactic shock. This syndrom is by no means a phenomenon of organism-sensitising, but merely a waste of the immunity phenomenon.

Antigen + antibody — choline + alexine = AAA complex (immunising) + ACh (paraphylactic shock).

At the same time, there is formation of an AA immunising complex, with antigens, which react without alexine (precipitines, agglutinines, antitoxines, a. s. o.)

Antigen + antibody — choline = AA complex (immunising) + ACh. (latent anaphylactic shock).

With antigens, which act with the concurrence of alexine, the acetylcholine genesis is intensive and rapid (explosive acetylcholine genesis); with antigens acting without alexine, there is slow and feeble acetylcholine formation (slow acetylcholine genesis). The AAA supplies the highest amount of ACh, which

elicits the shock. Consequently the shock which is named anaphylactic, is a paraphylactic acetylcholinic shock.

In organs, which are stimulated by the para-sympathetic and inhibited by the sympathetic (P + S-organs), ACh increases the contractility — which, in turn, increases the production of metabolites, that is, of histamine too.

Histamine, by an entirely different kind of action upon those organs, also increases their contractility.

The same thing happens with organs which are stimulated by the S and inhibited by the P (S + P-organs) as the heart and the vessels of systemic circulation.

The histamine, brought forth subsequently, elicits, similarly to ACh, a hypotension, which joins the acetylcholinic hypotension. But the mechanism which elicits this phenomenon is entirely different.

The shock is elicited by ACh, histamine being produced subsequently. Without ACh liberation there is no shock.

This is the mechanism of what we called a *complete immunity*, in which the whole antigen enters the complex AAA (or AA, for antigens reacting without alexine.) In the so called *incomplete immunity*, a part of the antigen is incompletely desintegrated and forms the *specific apotoxine*, as we called it; this one elicits the specific disease (serum malady, infectious diseases, a. s. o.).

Antigen + antibody — choline + alexine = AAA complex (incomplete immunity) + ACh (paraphylactic shock) + Specific apotoxine (specific malady-serum disease, a. s. o.).

The specific apotoxine, by its irritating action upon the conjunctive tissue, provokes the liberation of histamine.

It is well known that any mechanical, chemical or electric stimulation of the conjunctive tissue, produces histamine.

Consequently, besides the mechanism of histogenesis, which has been already mentioned, in the incomplete immunity we have a second mechanism, due to the specific apotoxine.

In the serum malady, the initial hypotension, the leucopeny with monocytose and eosinophily are of acetylcholinic nature, meanwhile the urticaria, the articular phenomena a. s. o. are specific phenomena, in which the histaminic action is very evident.

The acetylcholinic phenomena are very fugitive, meanwhile the lesion which histamine produces in the conjunctive tissue lasts more and dominates the clinical symptoms. But, chronolog-

ically, the liberation of histamine is of second order: without ACh, no shock, no subsequent histamine production.

Several authors have pointed out a very strong potassium liberation during the shock.

The fact which led into error those who have sustained the histaminic nature of the shock, is that histamine elicits phenomena which are very similar to those produced by ACh (stimulation of the digestive tract and of the uterus, hypotension) but the mechanism of which is entirely different. Though, histamine does not provoke cardiac inhibition, blood-hypocongelability, eosinophily and a series of other phenomena, which are characteristics of the paraphylactic shock, and which we have been able to call forth in normal animals by means of ACh.

Besides, atropine, which checks the ACh action and does not stop the histaminic one, prevents the paraphylactic shock.

The K^+ , which seems to be liberated in high amounts during the shock, provokes also certain symptoms, which are most similar to those elicited by ACh (stimulation of the digestive tract and of the uterus, hypotension). But atropine, which does not hinder the action of K^+ , but which checks that of ACh, stops the shock.

The conception of the histaminic nature of the shock has led the chemical industries to prepare drugs with a checking action upon histamine. But the substances which are called anti-histaminic and which we have utilised in our researches until now, make the cells of the end-organ refractory not only against histamine but also against acetylcholine and K^+ , which, as it has been told, provokes also certain phenomena, similar to those of the shock.

Until now we have examined the action of 2339 P—R¹ (antergan) and of 3777 P—R. Besides, we have studied the action of atropine and of pyramidon.²

Since 1943 we have proposed the following terms:³

ACh-checking of the parasympathetic action (ACh-P-checking) = which makes the cells of the E-o (end-organ) refractory against ACh.

¹ D. Danielopolu et collab. *Action de l'antergan*. J. de Phys. et de Path. Gén. 1941—1945.

² D. Danielopolu, Bull. Acad. de Méd. 1945 et Presse méd. 1946.

³ ACh-P-checking action = action parasympathofrénatrice ACh.
 A-S-checking action = action sympathofrénatrice A.
 K-P-checking action = action parasympathofrénatrice K.
 Ca-S-checking action = action sympathofrénatrice Ca.
 H-checking action = action histaminofrénatrice.

A-checking of the sympathetic action (A-S-checking) = which makes the cells of the E-o refractory against adrenaline.

K-checking of the parasympathetic action (K-P-checking) = which makes the cells of the E-o refractory against K^+ .

Ca-checking of the sympathetic action (Ca-S-checking) = which makes the cells of the E-o refractory against the action of Ca^{++} .

Checking of histamine action (H-checking) = which makes the cells of the E-o refractory against histamine.

The following table sums up their action:

Influence of drugs on the action of ...					
	Adrenaline	Acetylcholino	K	Ca	Histamino
2339 R—P	No action	Checking action	Checking action	Checking action	Checking action
3277 R—P	No action	Checking action	Checking action	No action	Checking action
Pyramidon	No action	Checking action	?	No action	Checking action
Atropine	No action	Checking action	No action	No action	No action

It results from this table that we have but one substance, which makes the cells of the end-organ against ACh, that is atropine. Atropine stops the paraphylactic shock which proves that ACh elicits the shock.

We see that 2339 P—R, 3277 P—R and pyramidon hinder not only the action of histamine, but that of ACh and of K^+ too — whereas atropine prevents only the action of ACh and not at all that of H and of K^+ . However atropine hinders the paraphylactic shock. Consequently it is clear that the shock is elicited by ACh.

The substances, which are called histamine-checking drugs, hinder at the same time the action of ACh and that of K. Because of this triple character, these drugs have an indisputable value in treating the paraphylactic accidents; they prevent also the action of K^+ and that of histamine. They are superior to atropine, which hinders but ACh, in the treatment of yet established paraphylactic accidents.

But the efficacy of 2339, 3277 and of pyramidon in the paraphylactic shock does not prove that the shock has a purely histaminic nature, because atropine, which prevents only the action of ACh and not at all that of H, also prevents the shock.

In the paraphylactic accidents of incomplete immunity, the histaminic phenomena, due to conjunctive lesions, are pregnant

and lasting. They mask the acetylcholinic symptoms, which are very fugitive. In the constituted serum-malady there is a moment when then only symptoms are the histaminic ones — and it would certainly be natural when a drug, which checks but the action of histamine, heals these phenomena.

Conclusions.

1. The paraphylactic (anaphylactic) shock is called forth by ACh. H is produced subsequently and has an important rôle, chiefly in paraphylactic accidents by incomplete immunity and specific apotoxine formation.

The histaminic effects, though secondary, are stronger and last a longer time. They command the clinical symptomatology, whereas the acetylcholinic ones, which are the first phenomena, are more fugitive.

2. The indisputable efficacy of 2339 P—R, 3277 P—R and of pyramidon, which prevent the action of histamine, does not prove that the paraphylactic shock is due to histamine, because these substances hinder the action of ACh as well.

3. The fact that atropine, which hinders the action of ACh without preventing that of H, prevents the paraphylactic shock, proves that this syndrome is called forth by ACh.

4. The substances, which are called anti-histaminic, are excellent medications in paraphylactic accidents, because of their triple action of hindering the effects of ACh, K^+ and H as well.

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Infection with *Actinomyces muris ratti* (*Streptobacillus moniliformis*) after Bite of Laboratory Rat.

By

L. O. BORGEN and V. GAUSTAD.

(Submitted for publication August 4, 1947.)

A. Clinical Part.

It is well known that bites of animals are capable of causing various, even severe infections. Rat-bites are considered particularly dangerous, and the Norwegian medical literature reports several cases of rat-bite fever and leptospirosis thus transmitted. In the present case the rat-bite is responsible for another and rare infectious disease, not previously diagnosed in this country.

On the 11th of December 1946 a woman of 25 years was admitted to Department VIII of Ullevål Hospital. On the 5th of December she had been bitten by a laboratory rat in the 3rd finger of her left hand. The patient is working in a laboratory for vitamin preparations and has often been bitten by rats without following signs of disease. This time the patient got symptoms of infection. On the 6th and 7th of December the back of her left hand and part of the forearm turned red and swollen. There was also a slight tenderness of the axilla. She stayed at home for some days and resumed her work on the 10th of December. But as she felt weak and uncomfortable, she had to leave work again the same day. The night before the 11th of December she had repeated chills and vomitings; she got a head-ache and had a slight pain in her back. She was admitted to the hospital on the 11th of December. Natural functions in order.

Apart from an attack of scarlet fever with uncomplicated course in 1929 and empyema of antrum on the right side after extraction of a tooth in 1945, the patient had always had good health.

Status praesens 11th of December 1946. The patient's cheeks were congested, and she complained of head-ache. Immediately after admission she had a chill. In connection with this the temperature rose to 40.2° C. A small, nearly healed wound after the rat-bite was seen on the 3rd finger of her left hand. Inconsiderable inflammatory reaction around the wound. No regional glandular swelling and no exanthema. Remaining physical examination revealed normal findings. On admission a blood-culture was taken, and treatment with sulfathiazole and penicillin was started. The patient received 1 g of sulfathiazole 6 times daily for 2 days, and 20,000 units of penicillin 8 times a day for 3 days. She had vomitings and felt rather weak, probably owing to the sulfathiazole medication. In the evening of 11th of December her temperature was 37.9° C. Later on she was afebrile and apparently well.

After leaving the hospital the patient complained of slight pains in her left arm. The pains were not localised to the joints, and it is possible that they have had no connection with the earlier infection.

Laboratory examinations: Urine normal. $11/12$ 46: Hgb. 98 %, R.B.C. 4.7 mill., W.B.C. 10,400 with diff. count.: 4.5 % stab nuclears, 81.5 % segmented forms, 10 % lymphocytes and 4 % monocytes. $14/12$ 46: W.B.C. 4,200. Colour of serum (McLengraecht) 1 : 2. Sedimentation rate 6 mm. W.R. \div . Electrocardiogram revealed right axis deviation.

On admission of the patient our diagnostic problems were concentrated on rat-bite fever, leptospirosis and possibly also an ordinary pyogenic infection. Immediate combined sulfathiazole-penicillin treatment seemed indicated.

The further course of the disease implied a slight infection, probably of pyogenic nature, and the report of a positive blood-culture was rather a surprise to the attending physicians. Identification of the micro-organism proved the presence of an infectious disease not previously diagnosed in Norway, and presumably not in the other Scandinavian countries. The isolated microbe proved to be *Actinomyces muris ratti*, also called *Streptobacillus moniliformis*.

Here a few remarks on rat-bite fever may seem reasonable. Rat-bite fever is caused by *Spirochaeta morsus muris*, sive *Spirillum minus*. Since about 1914 it has been known that not only the latter, but now and then also other micro-organisms are found in connection with infections following rat-bites. Most authorities, however, have been of the opinion that the presence of these micro-organisms was due to chance contamination, and with no causal importance to the actual disease. Only during the last years one has realised that bites of rats and partly also of other animals may cause two different infectious diseases of strikingly equal symptomatology. Moreover, besides sporadic manifestations after

bites of rats or other animals, the latter of the two diseases is also known to occur epidemically as food-infection. In 1926 an epidemic of 86 cases occurred in Haverhill, Mass. The disease is later named Haverhill fever or erythema arthriticum epidemicum. Place and Sutton (1) in 1934 gave a detailed description of this epidemic, that could be traced back to contamination of milk. There was no evidence, however, that the milk had been contaminated by rats or mice. Place and Sutton report a similar epidemic of about 600 cases in Chester, Pa., U.S.A. in 1925, studied by Armstrong and Wood. In 1939 Farrell, Lordi and Vogel (2) collected 14 cases from the literature, at the same time as they described one case observed by themselves, all cases occurring after bites of rats or other animals, and from which had been isolated micro-organisms similar to those found in erythema arthriticum epidemicum.

In 1945 Altemeier, Snyder and Howe (3) reported that in U.S.A. a total of 20 definite cases of erythema arthriticum epidemicum had been published, including their own three cases, all of them after bites of rats or other animals. The onset of erythema arthriticum epidemicum is acute, with chills, rise of temperature, vomiting and severe head-ache. In some cases there are slight prodromes, such as a general sensation of malaise, muscular pains and head-ache, lasting for a couple of days. The temperature, often rising above 40°C , falls to normal again after a couple of days. Feeling well, the patient tries to get up, but the recurrence of fever soon confines him back to bed again. The course of the fever is recurrent, similar to that of *Mb. morsus muris*, but in this disease the fever possibly has a more regular course. The fever lasts from a couple of weeks to several months. A rash appears from the 1st to the 7th day of the illness, most abundant on the distal part of the extremities, especially on the lateral areas, over the extensors and around the joints. It is seen on the palms of the hands and the soles of the feet, and often on the trunk and in the face. The eruption is maculo-papular with primary lesions with a diameter from 1 to 4 mm. The colour is deep red. Shape and arrangement of the eruption vary considerably. Usually it is like German measles, in some cases more like measles. It is often hemorrhagic, especially on the feet. The eruption lasts from 3 to 7 days. Also in *Mb. morsus muris* there is exanthema, but the primary lesions are usually larger, the extension being up to the size of a shilling.

Joint affection, of course, is an important symptom in erythema

arthriticum epidemicum. These symptoms are noticed on the 2nd to the 13th day of the illness, often marking the beginning of the recurrent fever. The severity of the joint affections varies from arthralgias to definite arthritis with swelling, rubor and exudate. The joints are very painful. Most common is affection of the wrists and elbows, next come knee-joints, shoulders, finger-joints and ankles. The duration of the arthritis is from a few days to several months. The joint exudate is yellowish, slightly cloudy, and microscopically showing polynuclear cells. *Actinomyces muris ratti* is demonstrated by bacteriological examination. Altemeier, Snyder and Howe (3) claim that duration of the arthritis may be very long, and mention 3 cases lasting 53 days, 8 months and more than two years respectively. Blood examinations reveal slight leucocytosis with some increase of the polymorphonuclears. During the disease there is hypochromic anemia.

Of the 20 cases diagnosed in U.S.A. up to 1945 (3) 2 were fatal. These were among the cases first diagnosed (Blake and Tumnicliff). Blake's patient died from endocarditis.

Clinical distinction between erythema arthriticum and common rat-bite fever is very difficult, and in his medical textbook of 1944 Osler declares: »the disease presents the unusual feature of having identical animal reservoirs, identical epidemiological spread and identical symptoms, but different etiologies.» Here the two diseases are considered a clinical entirety. Undoubtedly, however, two different diseases are represented. In 1940 Allbritten, Sheely and Jeffers (4) gave the following clues for differential diagnosis of the two diseases: Erythema arthriticum shows arthritis and an eruption of small primary lesions, whereas in rat-bite fever arthritis is rare and the primary lesions are larger. The incubation period for rat-bite fever as a rule exceeds 10 days, and for erythema arthriticum it is shorter. With the onset of rat-bite fever there is a renewed outbreak of the inflammatory changes in the wound, that often becomes chancroid. The bite of laboratory rats in most cases causes infection with *Actinomyces muris ratti*. The recurrent fever is more irregular in erythema arthriticum than in rat-bite fever. In a supplement to Nelson Loose-Leaf Medicine (5) erythema arthriticum has been described as a specific infectious disease.

The differential diagnosis, that always must be bacteriologically verified, besides a purely academical interest, also has therapeutic consequences. In *Mb. morsus muris neoarsphenamin* has very

good effect, whereas the result of this medication for erythema arthriticum is questionable. In the latter case penicillin seems to have good effect. According to Brooksaler the *Office of Scientific Research and Development* and the *National Research Council* have reported as doubtful the value of penicillin in treatment of infections with *Actinomyces muris ratti*. Later casuistic reports and experimental data, however, indicate favourable effect of penicillin. From the Mayo Clinic Heilman and Herrell have (6) published the results of penicillin treatment of experimental infection with *Actinomyces muris ratti* in mice. Without penicillin 96 % of the animals died. After penicillin treatment all the animals survived. Brooksaler (7), Weber and Favour (8) have reported 1 case each, Altemeier and associates (3) report 3 cases in which penicillin had immediate effect. Blood-cultures taken after institution of the treatment were sterile. Relapse in one of the cases of Altemeier and his assistants was attributed to inadequate doses. Wheeler (8) found 5 cases of rat-bite fever among 25 individuals bitten by rats. 4 cases showed infection with *Actinomyces muris ratti* and 1 with *Spirochaeta morsus muris*. 3 of the patients infected with *Actinomyces muris ratti* were treated with penicillin and with good results. The blood cultures that earlier had been positive, immediately became negative after institution of the treatment. During the treatment 1 of the patients developed an abscess, from which *Actinomyces muris ratti* was isolated. The abscess disappeared after one puncture. Also the patient with *Spirochaeta morsus muris* infection reacted favourably to penicillin treatment.

Our patient had a positive blood culture before the penicillin treatment. The fever promptly subsided and neither eruptions nor arthritis occurred. Whether this was a result of the treatment cannot possibly be decided. It may be permissible, however, on basis of the epidemiological data and the bacteriological results, to assume this to be a case of erythema arthriticum epidemicum, and the penicillin treatment possibly to be the cause of its abortive course.

In U.S.A. many authors consider *Actinomyces muris ratti* responsible for more cases of febrile infection after rat-bites than *Spirochaeta morsus muris*. Dawson and Hobby (9) point out that the growth of *Spirochaeta morsus muris* after inoculation of patients' blood into mice is insufficient for the diagnosis of Mb. morsus muris, because the mice beforehand may be infected with

this microorganism. The mice should therefore be accurately controlled before the inoculation.

B. Bacteriological Part.

On 11th of December 1946 the Bacteriological Laboratory of Ullevål Hospital received a citrate-blood specimen from the above patient, to be examined for *Mb. morsus muris* and Weil's disease. The bacteriological routine tests for these diseases gave no result.

A number of culture media were also inoculated with a view to the possibility of other infections. After 3 days there came growth in a blood broth culture. The micro-organisms grew in small, granular bottom colonies, gradually increasing up to the size of pin-heads. The colonies were mostly situated on the red blood-corpusele strata, but some were scattered somewhat up the walls of the flask.

Microscopical examination revealed a non motile, Gram negative, pleomorphic micro-organism, mainly consisting of short rods, some longer threads and coccus-like bodies.

Colonies were transferred to a number of liquid and solid media. Ascites-broth and serum-broth gave growth, but not plain broth. There was scarce, superficial growth on blood-agar, ascites-agar and Löffler's medium.

Both macro- and microscopically the growth on solid media morphologically was very different from the above description. The colonies were small and round, and especially in the serum-tubes, of a smooth character. Microscopically there were mostly long, looped filaments. These filaments were supplied with spindle-shaped thickenings on their ends as well as on the filament body itself. Some of the micro-organisms resembled spermatozoa, others were fungus-like filaments with interpolated spindle-shaped formations.

Examination thus revealed a highly pleomorphic microorganism with variations from tiny cocco-bacteria over coccus-like bodies to long actinomyces-like filaments. Most luxurious growth was seen on media containing both serum and red blood-corpuscles. No fermentation of carbo-hydrates.

The growth on Löffler's medium was easily emulsifiable in physiological salt solution, and made it possible to examine the serum of the patient for antibodies. 23rd of December 1946 the

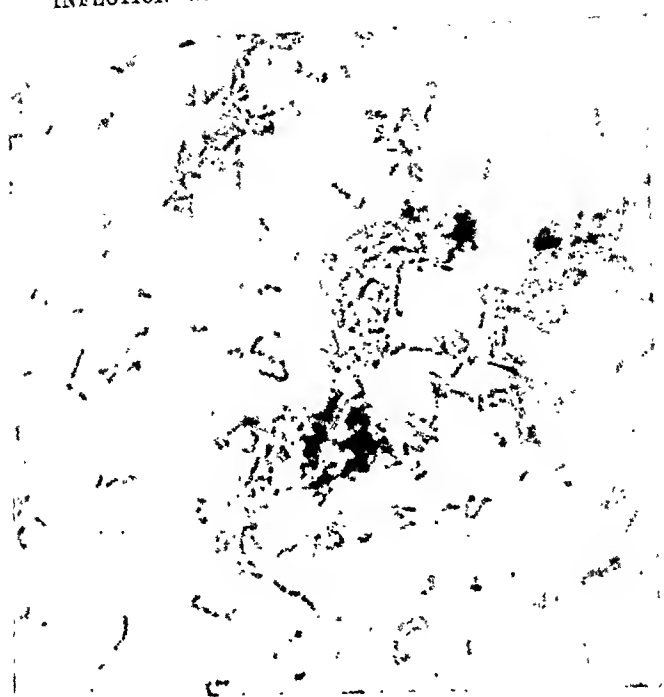


Fig. 1. *Actinomyces muris ratti* — bacillary phase.

Micro-photo $\times 1000$. Gram's stain after 72 hours growth in 10 % blood broth culture.

patient's serum gave a positive agglutination reaction with the isolated strain in a dilution of 1 : 80, whereas control sera did not give positive reaction in any dilution. A renewed agglutination test on the 9th of January 1947 was positive in dilution 1 : 96. These antibody titers are in fair accordance with antibody titers in earlier described infections with *Actinomyces muris ratti*.

Inoculation into guinea-pigs and white mice with the patient's blood, taken on 11th of December 1946 — the day of admission —, gave negative result. The isolated strain was inoculated into white mice and laboratory rats on 9th and 11th of January 1947 respectively. 23rd of January 1947 one white mouse showed definite signs of infection. It was lying on its side, the hind legs drawn up, and gasping for breath. It was killed, and cultures made from blood, spleen, liver and kidneys. A few days later the inoculations into blood-serum-broth gave definite growth. Up to now the laboratory rats have not shown any signs of infection.

The first description of such bacterial infection after rat-bite was given by Schottmüller (10) in 1924. He named the microbe *Streptothrix muris ratti*. He also demonstrated a similar microbe

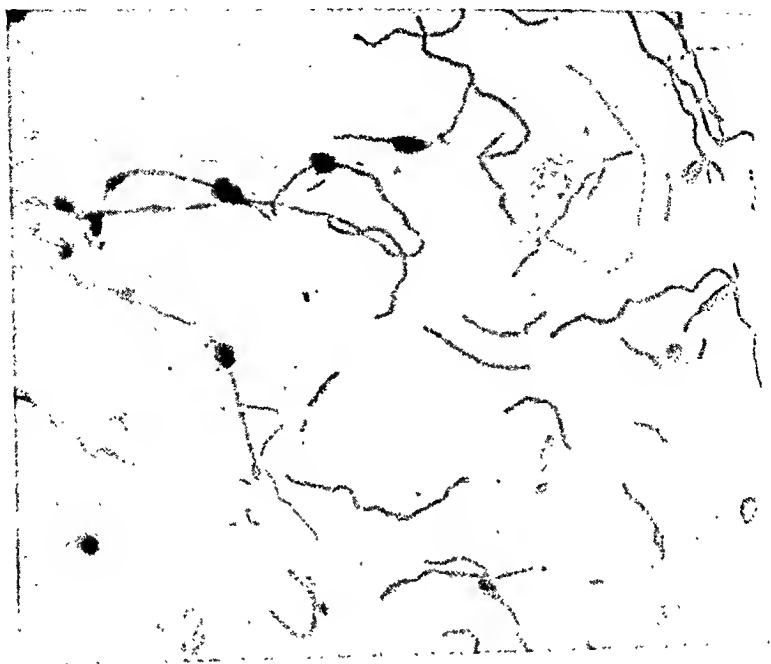


Fig. 2. *Actinomyces muris ratti* — moniliform phase.

Micro-photo $\times 1000$, Gram's stain after 24 hours growth on Löffler's medium.

after bite of a South-African squirrel. This one he named *Streptothrix taraxeri cepapi*. Later on *Streptothrix muris ratti* has been found also by others in connection with bites of rats and other animals; thus Nixon (11) in 1914 described a case after bite of a ferret, the result of the bacteriological examination is not reported. In 1916 Blake (12) described a case of rat-bite infection with lethal issue. The microbe of this infection was isolated from blood, and valves of the heart, which showed an ulcerous endocarditis. The same year Tunnicliff (13) demonstrated a similar streptothrix in domestic rats with broncho-pneumonia. In 1918 Dick and Tunnicliff (14) isolated a streptothrix from the blood of a patient bitten by a weasel. They named the microbe *Streptothrix putorii*.

In 1926 Levaditi and his associates (15) found the same microbe in a laboratory assistant bitten by a laboratory rat. He gave it the name of *Streptobacillus moniliformis*, which is the name that is now most commonly used for this micro-organism.

In 1926 Parker and Hudson (16) use the name of *Haverhilli multiformis* for a microbe found in connection with Haverhill fever, also called *Erythema arthriticum epidemicum*. This microb

has proved identical to *Streptobacillus moniliformis*, making a total of 4 names for *Actinomyces muris ratti*.

In several of her works Klieneberger (17) (18) has pointed out, that the microorganism in question is not one, but two micro-organisms living in symbiosis. One of them is an extremely fine, small organism that pass through coarser bacterial filters. This one she terms *L. organisms*.

This *L. organism* Klieneberger claims to be closely related to the group of micro-organisms producing pleuro-pneumonia *bovis*. This filtrate form, she believes, can be isolated in pure culture from *Streptobacillus moniliformis* strains. In pure culture *Streptobacillus moniliformis*, on the contrary, is supposed incapable of reproducing the filtrable form.

This view has been energetically contested by Dienes (19) who in 1939 declared it to be a phenomenon of bacterial variation. The dispute has not yet been concluded.

Summary.

A laboratory assistant developed signs of lymphangitis and lymphadenitis shortly after being bitten by a laboratory rat. The infection rapidly improved, but 6 days after the accident the patient had chills and was sent to the hospital in high-febrile condition. On combined sulfathiazole and penicillin treatment the fever subsided at once. From blood cultures, taken before starting the treatment, *Actinomyces muris ratti*, also named *Streptobacillus moniliformis*, was isolated. The isolated microbe demonstrated the same morphological and cultural qualities as earlier described strains. Examination of the patient's blood for antibodies 12 days after beginning of the high-febrile state, showed positive agglutination test in dilution 1 : 80. No case of infection with *Actinomyces muris ratti* after bites of rats has earlier been described neither in this nor in the other Scandinavian countries.

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A Contribution to the Knowledge of the Frequency of Thyrotoxicosis in Finland during the Years 1935—1946.

By

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Introduction.

The variation in the frequency of thyrotoxicosis during different periods and under different external conditions has been the subject of numerous investigations. It seems as if particularly post-war conditions had aroused new interest in the question. Firstly, there is the lack of food caused by the war which, thanks to rationing in the majority of countries, can be fairly well surveyed and estimated. If alimentary factors play a rôle, on the whole, in the origination and development of thyrotoxicosis the abnormal conditions prevailing during and after the war cannot have passed by without leaving traces. Another factor in modern total war which may influence the frequency of the disease is represented by psychical strain which almost the entire population in the countries at war has been subjected to. On account of a change being stated in the frequency of thyrotoxicosis, in some quarters in Finland — principally a decrease in the number of cases of thyrotoxicosis — I have, encouraged by Dr J. Wahlberg, examined the thyrotoxicosis material in the general hospitals in Helsingfors during the years 1935 to 1946.

A similar study was made after the First World War by Tallqvist who classified the cases available to him during the years 1916 to 1922. He stated a decrease in the frequency starting from 1916

and reaching ground level in 1918—1919 and rising again rapidly in 1921. An interesting fact is the coincidence of the period of decrease with that of a crisis in food supplies. Tallqvist did not hesitate to consider this fact, and holds that it might motivate certain conclusions even regarding internal treatment of thyrotoxicosis.

In the interval between the two wars the frequency of thyrotoxicosis was on the increase, on the whole (Borak, Firgau, Wiesel and others). Sällström, Sweden, who examined an extensive series, dating up to 1932, observed a regular increase of the number of cases year by year. He believed that the reason thereof was the improved diagnostic and that the patients were more often sent to hospital but also an absolute increase of the morbidity.

Some papers dealing with this question have been published during and after the Second World War. Meulengracht stated, in Denmark, an accumulation of cases in 1942. He could give no definite reason for this occurrence, however, and it should be observed that Denmark does not belong to those countries in which the lack of food was particularly great. In Holland, Schweitzer observed a steep decrease in the frequency from 1942 on, and simultaneously a general decrease in the metabolic level of the population. He points out that these circumstances coincide with the critical time in food conditions in that country. Finally, Grelland stated that the frequency of thyrotoxicosis in Norway rose from 1934 to manifold in 1941, decreasing again to below the pre-war level in 1944. The reason for an increasing frequency before 1941 is, according to Grelland, an increased consumption of proteins, the decrease in the frequency after 1942 might be due to the difficult conditions in respect of foodstuffs, while the peak in 1941 may be explained to be due to psychical factors owing to the war.

Summarizing we may say that it seems as if there were an increasing frequency of thyrotoxicosis during the time between the wars. It is difficult to judge whether the increased frequency was caused only by an increased hospitalization, or if also alimentary factors have played a rôle. Information from the time of the Second World War is contradictory to a certain extent, as mentioned. It seems, however, as if the thyrotoxicosis morbidity had decreased in the countries experiencing difficulties with food supplies.

The Author's Own Series.

My series concerns the years 1935 to 1946. The reason for choosing this period of time is because of a good picture of the abrupt changes in the conditions of life brought about by the war, being obtained in these years. In 1935 to 1939 there was a gradual improvement in the standard of living in Finland following the economical crisis in the beginning of the 30's. The food situation was good at this time and nutrition was rich in calories, varied, and contained sufficient amounts of protein. The years 1940—44 were times of war, but the food situation was fairly satisfactory still in 1940—41. At the end of 1941 a change for the worse set in in this respect. The rationing lists of the Ministry of Supplies show that the daily supply of calories was catastrophically reduced just at this time. Meat and fat rations in particular were much reduced and the lack of calories arising on this account was inadequately compensated by a slightly increased supply of carbohydrates. Although a decided improvement was observed in 1942 to 1944 it may be said that the conditions were unchanged on the whole. This was the case in the first post-war year, 1945. An improvement set in in 1946 when certain foodstuffs were liberated from rationing, but there was still no question of normalization, however. Despite the fact that the rationing lists of the Ministry of Supplies do not give an exact picture of the true conditions, owing to the wide-spread illegal market with foodstuffs, of the amounts used per day, they illustrate however fairly exactly the deterioration in the food position during the war years.

The patients in my series were collected from all the general medical and surgical departments of Helsingfors City Hospital and of the General Hospital of Helsingfors, and all cases diagnosed thyrotoxicosis, Morbus Basedow, or corresponding diseases were included. As the majority of these hospitals are University clinics I have set out from the diagnoses being as reliable as can be expected. A great number of the patients had been treated several times for their disease or had been removed from a general medical to a surgical department, and vice versa. These patients are included once only in the series. The patients treated at Helsingfors City Hospitals are all townspeople and those treated at the General Hospital of Helsingfors are in the majority country people.

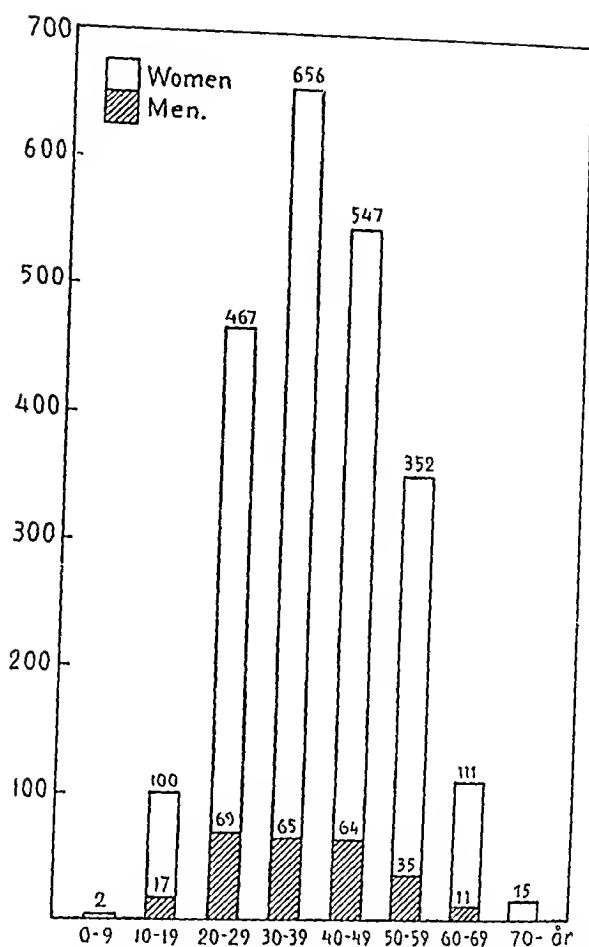


Diagram I. Distribution according to age and sex of thyrotoxic patients in the general hospitals of Helsingfors in 1935-46.

For the purpose of analysing more closely the kind of cases which are included in the series I have noted the cases with exophthalmus separately. For the purpose of differentiating characteristic cases to some degree, I have calculated the cases which showed 5 or 6 of the following symptoms: distinct loss of weight, eye symptoms, tremor, abnormal sweating, tachycardia, diarrhoea. These typical symptoms of thyrotoxicosis are presumably included even in scanty hospital reports. Although this procedure will not give an exact picture of the conditions it may however give an idea of the frequency of severe cases in the fairly extensive series. An opinion based on the basal metabolic values cannot be considered justified as they were determined

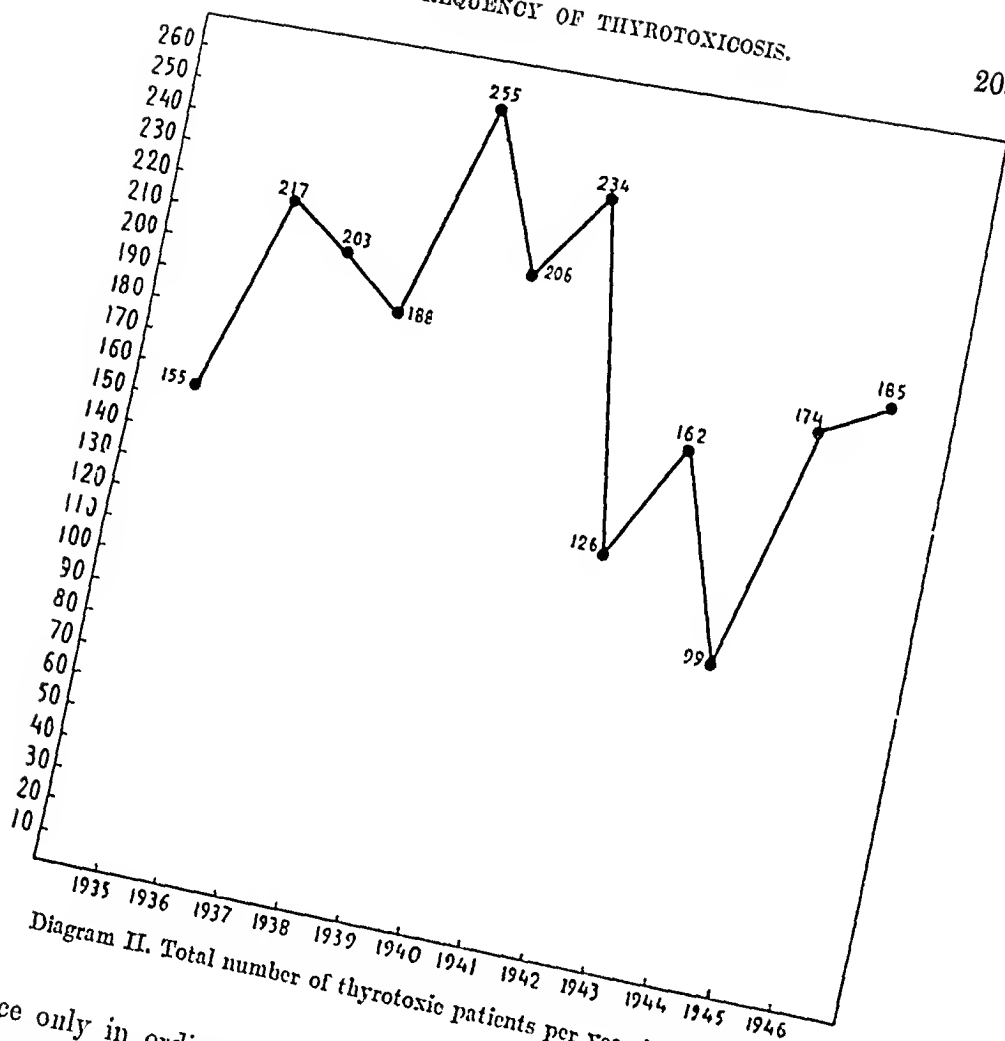


Diagram II. Total number of thyrotoxic patients per year in 1935—46.

once only in ordinary routine examination, in the majority of the cases. Such routine values are of practically no importance in appreciating the thyrotoxic cases (Wahlberg, Thompson, Biström).

A total of 2,114 thyrotoxic patients were treated in the mentioned hospitals during the years 1935—46. There were 241 males which somewhat more than 11 per cent of the total series of thyrotoxic patients. The age distribution reaches a maximum between 30 and 40 years (Diagram I), which agrees well with corresponding figures given by Sällström. It may be mentioned that only a very small number of the patients were treated in internal medical departments; the great majority were treated only in surgical departments.

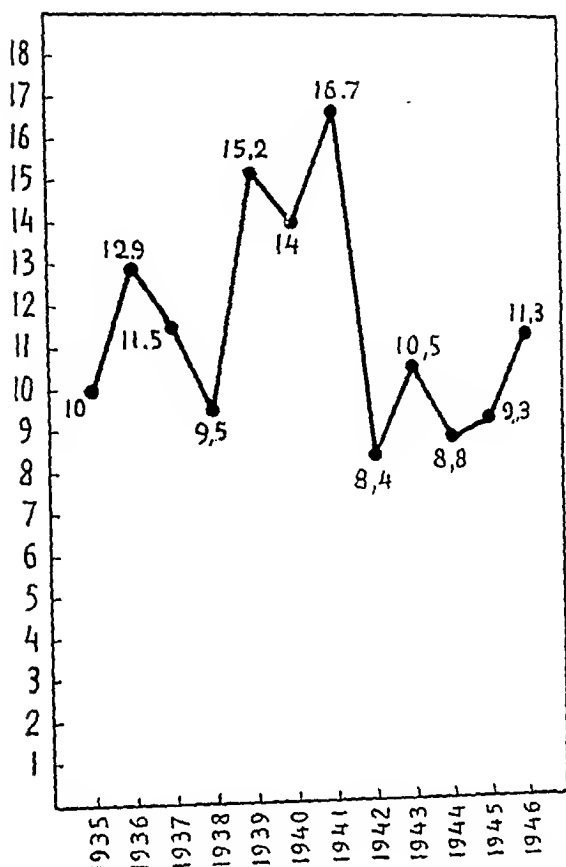


Diagram III. Number of thyrotoxic patients, per mille, in relation to the number of patients treated in the hospitals in 1935—46.

Results.

The results are seen clearly from the appended diagrams. Diagram II gives the total number of treated cases of thyrotoxicosis. As seen from the diagram there is an increase during the years 1935—39 and the maximum is reached in 1939. The values for 1940 and 1941 are almost as high, although somewhat lower than for 1939. There is no mentionable difference, however. In 1942 there is a steep decline in the curve and the level is lower than in the years immediately preceding the war. In 1946 there is a certain increase.

Diagram III gives the number of thyrotoxic patients (per mille) in relation to the total number of patients treated in the

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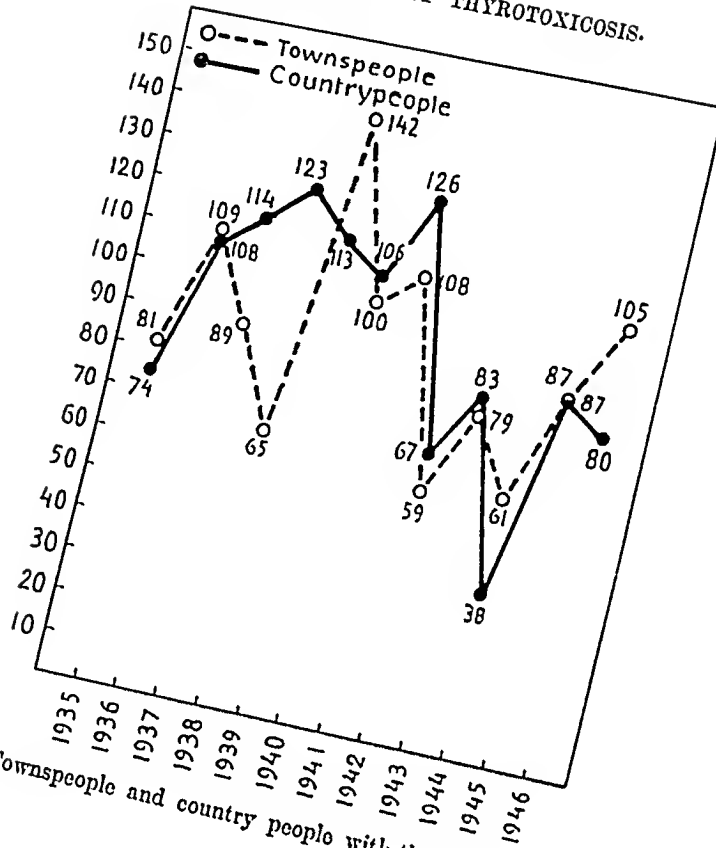


Diagram IV. Townspeople and country people with thyrotoxicosis in 1935—46.

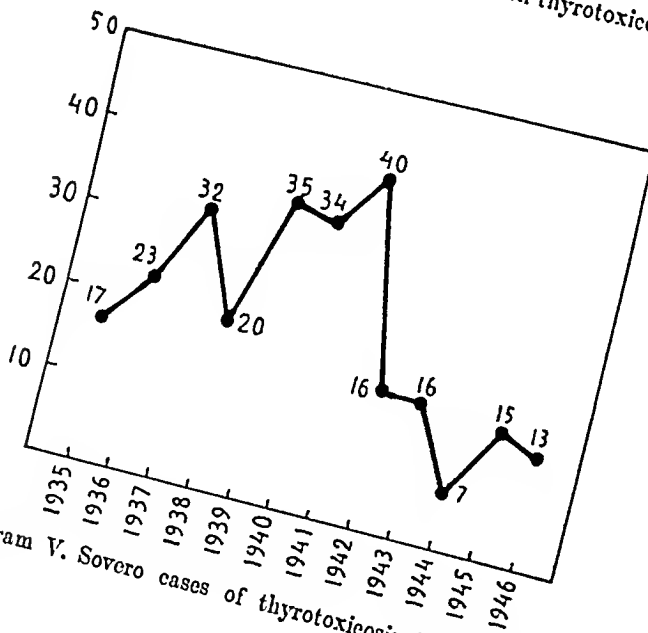


Diagram V. Severe cases of thyrotoxicosis in 1935—46.

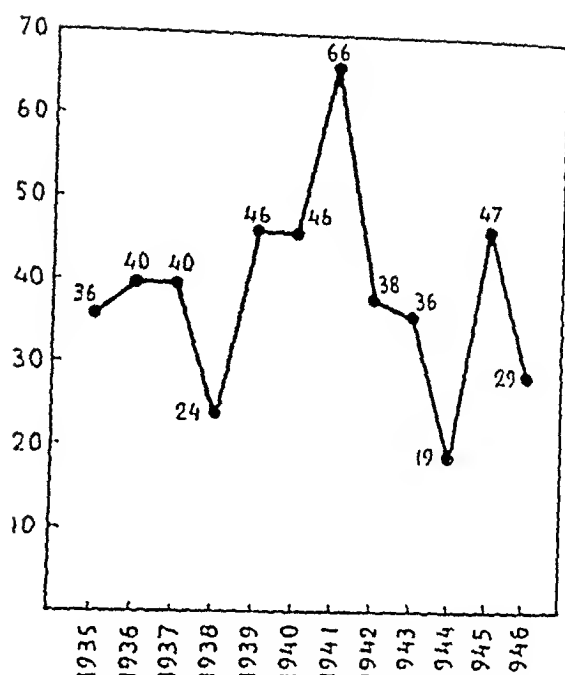


Diagram VI. Thyrotoxic cases with exophthalmus in 1935—46.

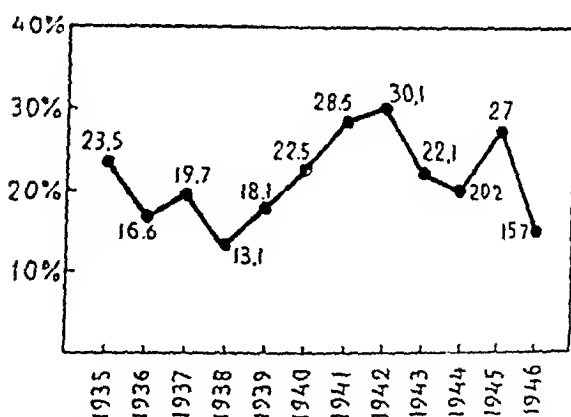


Diagram VII. Number of cases with exophthalmus, in per cent, in relation to the total number of cases of thyrotoxicosis in 1935—46.

hospitals. The curve shows the same tendencies on the whole as does the curve in Diagram II but the maximum is reached in 1941. An increase is observed in 1946.

Diagram IV comprises country people and townspeople separately. As seen, the two groups do not differ to any extent

but the frequency of townspeople is, however, somewhat more irregular. The curves proceed approximately as does the curve in Diagram II.

Diagram V concerns the severe cases which reach their maximum in 1941. During the years 1935—41 the frequency increases but pre-war values are not attained even in the years 1942 to 1946. The minimum is observed in 1944.

Diagram VI gives the number of patients with exophthalmus. An absolute maximum for these cases is noted also in 1941, while the values for the years 1942 to 1946 are in general lower than before the war. 1945 is an exception as the number of cases is fairly large in that year.

Finally, Diagram VII gives the number of exophthalmic cases (in per cent per year) in relation to the total number of thyrotoxic patients. The curve is irregular and peaks are reached in 1935, 1941, 1942, and 1945 and shows low values for the years 1938 and 1946. The percentages vary between 13.1 and 30.1.

Comment.

This investigation shows that the number of thyrotoxic patients treated in the mentioned hospitals has decreased since 1942. Simultaneously the number, calculated per mille, decreases in relation to the total number of hospitalized patients. In 1946 an increase is observed but pre-war values are not attained. It is very difficult, however, to determine what rôle the greatly disturbed conditions in the hospitals during the war play in this respect. Some of the departments investigated were used for care of the war-wounded. Furthermore, a number of patients probably avoided treatment in hospital on account of the uncertain conditions prevalent. The decrease in the frequency must, without doubt, be partly due to these circumstances particularly in the years 1942 and 1944.

The fact that there was no decrease in the frequency during the first two war years, 1940—41, when conditions were equally disturbed in the hospitals and that the decrease continues during the post-war years 1945—46, when conditions were normal again in the hospitals, speaks for other factors also having been of import. If the patients, due to lack of berths during the war, were not admitted into hospitals or, if, due to uncertain conditions they avoided the hospitals, the first war years would have shown a

great increase in the number of cases. The characteristic cases also showing a similar tendency to decrease supports what has been said above. Treatment in hospitals is of greater importance for these patients than for the mild cases, and their number should, in any case, have increased during the quiet intervals. In addition we have a reduction in the number of thyrotoxic patients in relation to the total hospital material in 1942—46. All this is a sign of other factors being influential as well in the decrease of frequency, besides the abnormal hospital conditions caused by the war. These factors have evidently come to the fore in 1942 and still play their part in the post-war years, 1945—46.

Should importance be attached to psychical factors during the war in Finland in these respects? Undoubtedly the majority of the people lived under strong psychical pressure during the years 1940—41. A large part of the population took part in active warfare but also on the home-fronts the people were subjected to much greater psychical strain than general, for instance on account of the constant bombing raids, anxiety for relatives at the fronts, difficulties with food and clothes, etc. According to earlier general conception psychical factors were considered to play a significant part in the origination of thyrotoxicosis. Lately a variety of opinions have been heard, however. Means, for instance, is not certain of cause and effect. In the epidemical increase of the disease in Denmark, psychical factors which might have been predisposing were found by Meulengracht only in a few instances. Simultaneously with the general exposure to psychical strain during the war a decrease in the frequency of thyrotoxicosis was stated in Finland.

A fact that is remarkable and which may hardly be incidental is that the restrictions in food supplies coincide exactly in time with the decrease in the number of thyrotoxic cases. The lack of food prevailed unchanged, on the whole, and did not improve before 1946. The number of treated cases of thyrotoxicosis was also low and increased somewhat in 1946. This is analogous to Tallqvist's statements from the time of the First World War, to Schweitzer's reports of to-day from Holland, and to Grelland's from Norway.

Food conditions in Finland in 1942—46 were characterized, as mentioned, by a decrease to the minimum of the daily supply of calories. Meat and fat rations were greatly restricted at the same time. The caloric lack was partly compensated by food containing

carbohydrates. In an endeavour to find out which of these facts may have influenced the thyrotoxic morbidity, the reduced protein consumption should be considered in the first hand. It has already been stated that a diet rich in proteins increases the metabolism and the secreting activity of the thyroid gland (Bomskov). In dietetic treatment of thyrotoxicosis the supply of protein is generally reduced (Wahlberg, Barr). In addition there is a reduced supply of calories as well. Malnutrition tends to decrease the activity of the thyroid gland, as is well known (Bomskov, Loevi).

On the basis of the facts given above the variations in the frequency of thyrotoxicosis might be explained as follows:

During the prosperous pre-war years, 1935—1939, when the food situation improved more and more, and the food in Finland was rich in calories and in protein the thyrotoxic disease increased slowly. After 1942, when lack of foodstuffs pressed down the supply of calories the number of cases of thyrotoxicosis decreased, and in 1946, with an improved food situation, a slight tendency towards an increase in the frequency was observed. These statements support the opinions put forward by Tallqvist, Schweitzer, and Grelland. Yet we can hardly suppose that the mentioned alimentary factors would have anything in common with the fundamental causes of thyrotoxicosis. The activity of the thyroid gland decreases when the consumption and the supply of calories is reduced, and this naturally affects thyrotoxicosis in that the mild cases may actually become free from symptoms and the severe cases modified.

It is difficult to state, on the basis of this study, whether the factors mentioned may be of consequence in dietetic treatment of thyrotoxicosis, but the results of the investigation support the common conception that a reduced supply of proteins is beneficial in thyrotoxicosis. The supply of calories should be plentiful because the consumption of nourishment increases with elevated basal metabolism. Tallqvist certainly says that he has not observed any favourable results with fattening-therapy in thyrotoxicosis. He considers that the disease has its given course in any case. The majority of investigations show that lack of food is in general connected with a decrease in the morbidity of thyrotoxicosis.

Conclusions.

1. *A decrease in number of thyrotoxic cases was observed in the general hospitals of Helsingfors in 1942—46.*

2. *The decrease of the frequency is evidently due to abnormal conditions in the hospitals caused by the war, but it seems as if also a true decrease of the thyrotoxic morbidity were present.*

3. *The decrease observed in the frequency of thyrotoxicosis coincides, regarding time, with the lack of food caused by the war — characterized by a greatly reduced supply of calories, particularly of proteins and fat in the food.*

4. *An acceptable reason for the decrease of the frequency may be the greatly reduced protein consumption. The decreased supply of calories may also play a certain part.*

5. *An increase of the frequency due to psychological strain during the war was not observed.*

Summary.

Biström has studied the frequency of thyrotoxicosis in the general hospitals of Helsingfors during the years 1935 to 1946. In 1935—39 a tendency towards an increase in the number of cases was stated. The frequency was unchanged on the whole in 1940—41, a great decrease was observed in 1942, and a slight tendency towards an increase in 1946. A similar curve was obtained for thyrotoxic patients, calculated per mille, in relation to the total number of patients treated in the hospitals. Also the severe cases and those with exophthalmus decreased during the years 1942 to 1946. No great difference in the frequency between townspeople and country people was observed.

The abnormal conditions in the hospitals during the war is assumed to be one of the reasons for the decrease of the frequency. As there is no increase in the number of cases — to pre-war level — during the calm period of the war, or during the first two post-war years, 1945—46, a true decrease of the morbidity is considered present.

As the lack of food in 1942—46 coincides, regarding time, with the mentioned decrease of frequency this is probably the actual causative factor. The reduced protein consumption is decisive

in this respect but the diminished daily supply of calories may also be influential. No increase of the frequency of thyrotoxicosis, due to additional psychical strain during the war, was stated.

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SVEN INGVAR (1889—1947.)

Sven Ingvar, professor of practical medicine at the University of Lund, died April 21st 1947 in his home in Lund. The cause of death was encephalopathia hypertonica, the ultimate complication of a severe malignant hypertension which had interfered with his health for the last years. Sven Ingvar became only 57 years old. He was born Dec. 15th 1889 in Denmark, where his father was a Swedish land-owner whereas his mother was Danish by birth. The family settled over to Scania, the southern province of Sweden, where Sven Ingvar went to school in Ystad. Having absolved his maturation examination in Ystad he entered the university of Lund, where he in due course performed his medical studies, encouraged not least by his friend and teacher in medicine, Karl Petrén. In Jan. 1919 — how well I remember the glittering snow and the shining sun of that morning of his Austerlitz — he defended his thesis for the degree of doctor of medicine, a thesis which was to become known all over the globe, «Zur Phylo- und Ontogenese des Kleinhirns». This thesis made him docent (associated professor) in neurology and eventually he succeeded Karl Petrén as professor in practical medicine, in Nov. 1929, thus before the age of 40. He had, thence, the privilege — and the burden — of representing the main subject of the medical studies until his untimely death.

The research of Sven Ingvar was mainly devoted to neurology, a topic which in Lund fortunately always has been united with general medicine. The monumental work was, of course, his thesis but he had already earlier given his attention to cerebellar problems, having published in 1916 a paper on the importance of cerebellum for speech. On the suggestion of Karl Petrén he went as a young man to Ariens Kappers in Amsterdam, who gave him the problem of the phylogenetical relationships of the cerebellar structures, with special regard to the comparative anatomy but pertaining also to the physiology and the clinical pathology of cerebellum, not least with regard to the localization. Working along the lines of comparative anatomy, experimental anatomy and embryology, Ingvar managed to tackle the giant-sized problem and to outline the principles of cerebellar phylogeny and

cerebellar localization as we know them to day. He was able to demonstrate the development of cerebellum as a differentiation of the vestibular nuclei and to disentangle the difficult questions of the importance of cerebellum with regard to our behaviour in space. The results of this investigation were published in the thesis just mentioned and turned out to be of fundamental importance for our interpretation of the cerebellar activities, being amply confirmed by later research on the subject, thus recently also by a study on the electrical activity of the cerebellum and its functional significance, by Dow.

The general problems connected with the localization in the central nervous system attained the interest of Ingvar already in his thesis, where the cerebellum became the test tube in which the problem was concentrated. Working upwards, he continued with the thalamencephalon and eventually also with the cortex of the telencephalon, the pallium of the hemispheres. Already when cerebellum was concerned Ingvar arrived to a conception which proved to be extremely fertile for future research. He maintained that when a certain area or surface was given, a new acquisition to this area always was to be encountered in its center, whereas the phylogenetically more ancient structures were to be found in the periphery as a margin around the recent achievements. Thus, in cerebellum, the neocerebellar hemispheres were developments from the middle (central) part of the phylogenetically old cerebellar structures. As for thalamencephalon a special application of this principle was ascertained by Ingvar with regard to the optic pathways. The reaction of the pupil to light represents a phylogenetically old principle and the corresponding pathways are accordingly to be found on the surface of the organ, where they are exposed to meningitic injuries, whereas the reaction of the pupil to convergence is a comparatively recent achievement and accordingly to be found in more central and hence less exposed structures. This explanation tallies well with the well-known Argyll-Robertson phenomenon, which is to be observed in various meningitic disorders, not only in connection with syphilis. Corresponding points of view were, according to Ingvar, to be applied to the superficial localization of those fibers of the oculomotor nerve which are concerned with m. levator palpi. Particularly, however, is the general conception thus arrived at to be applied to the localization in the cerebral cortex. Ingvar maintained rightly that if the cerebral hemisphere is con-

sidered as a surface and accordingly developed in one plane, the ancient structures, such as the rhinencephalon, are to be found in the periphery of this surface, whereas the recently achieved strictly human abilities, such as the stereognosis of the hand, the speech and the binocular seeing are represented in the center of the cortical surface. This apprehension has turned out not only to be of theoretical interest but of outstanding practical importance for the clinic. It is entirely in line with this general conception that the cortical representation of the old monocular visual field, the so-called temporal crescent, later has been found rather near to the periphery of the pallium, at the confluence of fissura calcarina and fissura parieto-occipitalis (Ask-Upmark, in a paper from the clinic of Ingvar). The old entangled conception of more or less strictly different types of aphasia did not satisfy Ingvar, who was able from the point of view here stressed to get a more general aspect on the problem. One may surmise that he thoroughly enjoyed this conception for, whereas too many neurologists are men of details, Ingvar, whilst diligent and ambitious in his work and no friend of sweeping statements, was a man who liked broad aspects, simplicity when compatible with facts and fresh air above the problems.

Among other important neurological contributions may be mentioned the studies of Ingvar on the subarachnoid haemorrhages, where he, in 1918, was the first to describe the ruptures of the elastic tissue in the arteries on the base of the brain. The embryology of the sympathetic nervous system, was examined by Ingvar together with Erik Müller and its derivation from the ganglion crest was definitely established. Questions of more immediate clinical application that were tackled by Ingvar may be exemplified by the leaking of cerebrospinal fluid into the epidural space after lumbar puncture, and the strangulation of the brainstem by means of the flocculi cerebelli in foramen magnum.

Most of Ingvars neurological studies were performed before his denomination to professor in practical medicine. As unfortunately most clinical professors in this country he had, thence, to assume the burden of considerable medical teaching and administration. Nevertheless he managed to publish an important paper on cicatricial pericarditis and he took a vivid interest in problems with bearing on health menaces of the people, such as the rheumatic disorders and the chronic ethylism. With regard to the rheumatic diseases he rightly maintained that the most important

step to be taken in order to fight these disorders in Sweden was the establishment of more medical departments in our provincial hospitals and more orthopedic departments in our central hospitals. Just as another great neurologist, Victor Horsley, Ingvar became absorbed by the problem of the alcoholism and devoted much time and effort to this much neglected part of the practical medicine. An outstanding piece of work during the last decade of Ingvar's life was his study on the metabolic gradients. These questions had absorbed his interest already when he as a young doctor went to the United States, doing commendable work in New Haven. His thesis, supported to some extent by earlier investigators such as Child, Coghill and others, was that a more cranial segment of the body as a rule had a more vivid metabolism than, *ceteris paribus*, a more caudal segment. He was able to collect a considerable clinical material with bearing upon this problem, which by the way also pertains to other important questions, such as the predilection of polyarthritis to the right hand in righthanded people. The results of this investigation were presented to a medical meeting in Stockholm but the disease unfortunately prevented him from publishing the details. It may be said, however, that the character of the problem was extremely characteristic for Ingvar's pattern of research: to tackle difficult problems along broad supervisable lines and by means of his sparkling genius to gain results applicable to a fascinating multitude of practically important clinical questions.

Sven Ingvar was an excellent clinical teacher, not least so for the more advanced students. His memory, his criticism, his ability to distinguish between important and less important facts, his broad and deep knowledge of his subject would have made him a good instructor anyway. When clinical matters are concerned no intellectual qualities will, however, be sufficient if not united with a sense of responsibility and a kind and deep human interest in the patient. Ingvar was no friend of words and he was particularly afraid of big and fat words about ethics, as they sometimes unfortunately have been put forward by the zelots, yet he managed to give an excellent instruction not only in the knowledge of the medical topic — he sometimes stated that no ethics be sufficient for a doctor if not supported by medical knowledge — but, by means of his own manners, also in nice and decent bed side behaviour and in broad human understanding of the patient, his personal difficulties and his social background. The skilled brain,

the tender heart and the soft hand made him not only an excellent scientist, not only a brilliant medical teacher but last but not least a good doctor.

It was the ambition of Ingvar always to let his clinic maintain a place in the very front line of medicine. His international reputation and his stimulating spirit greatly facilitated these efforts, the visible fruits of which were the numerous scientific publications from the clinic. It was entirely in line with his own character that he in every way encouraged international scientific relations. He went abroad himself repeatedly, as a young man for studies in the Netherlands and in the United States, later being called in to give the Herter lecture in Baltimore and the Hunter lecture in England. A visible sign of the appreciation of his work was given when the Rockefeller Foundation bestowed upon him the facilities for establishing a neurological laboratory, to be forthwith connected with the medical clinic.

Sven Ingvar was personally a kind, broad-minded man, a man of humour and wisdom, a man more able to unite natural sciences with true humanism than most people we have had the privilege to meet. He was the faithful friend of his many friends, the enemy of nobody. He was in harmony with his job, in harmony with life itself, a fact greatly facilitated by his happy family life. He was married twice, when quite young to his first wife, who soon died, and afterwards to a daughter of Salomon Henschen, with whom he had three children and a most happy home, open as his own heart to his friends. He despised unjustness whenever encountered. There was always around him, until the disease turned him down the hill, that brilliant sparkling of youth, and flowers grew along his path through this world.

One may look upon life as a continent, where we start the travelling at the coast, the phylogenetically older region, the cradle of life, and attempt to proceed inwards. Some of us go astray, parallell to the shore or back to it, some of us remain camping in the woods but there are also people who proceed towards the middle of the continent, the convexity of the hemisphere, the true human region. We may not reach the very center, the Montsalvat, but we may be thither bound. Sven Ingvar belonged to the last category. He sought clarity. He brought us knowledge. He was a good man.

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On the Mechanism of Glycosuria. I.¹

By

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(Submitted for publication June 16, 1947.)

Claude Bernard demonstrated in 1877 (2) that glucose is a normal constituent of the blood and that it does not pass into the urine till the blood-sugar exceeds a certain limit, the so-called »sugar threshold». In 1885 von Mehring (19) was able to show that phlorizinisation is capable of inhibiting the ability of the kidney to retain the glucose, so that glycosuria may arise when the bloodsugar is normal. It was not until the years round about the first World War that developments within the sphere of microchemistry permitted of more routine tests of the sugar in the blood, including its connection with glycosuria. In Denmark, contributions towards the elucidation of the problems have been made by Aage Th. B. Jacobsen (17), Faber & Norgaard (7), Hagedorn (11), Karen M. Hansen (6), J. E. Holst (16), and other Scandinavian investigators include Engstrand (5), Petró (21) and Hatlehol (14).

In his thesis for the doctorate (12) (1921) Hagedorn published the first graphic computation (fig. 1) of simultaneous blood and urine-sugar analyses from a diabetic. It shows that at a point a little above the threshold the glycosuria seems to be proportional to the level of the blood-sugar, the points falling in a straight line; on producing this line downwards its point of intersection with the abscissa will show the position of the »line threshold». (On the line threshold, see below.)

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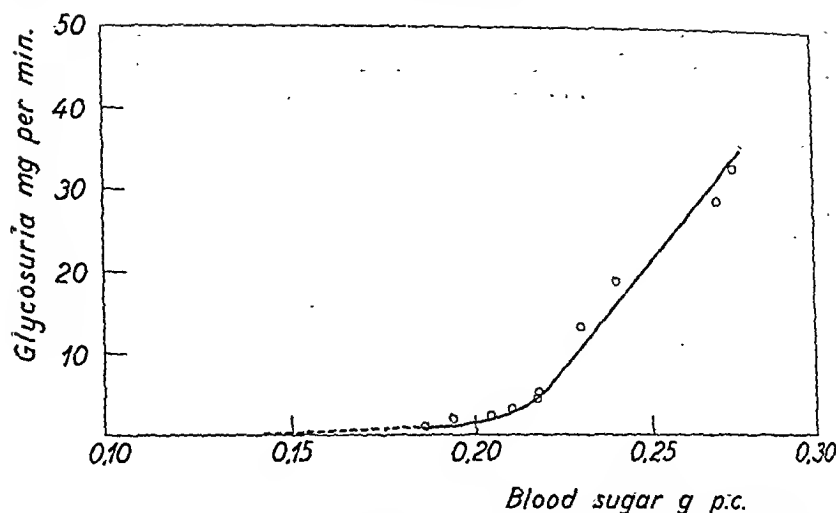


Fig. 1. Blood-sugar and urine-sugar in diagram. (From Hagedorn's dissertation.)

The filtering function of the kidney in respect of glucose could not be comprehended to the full until the filtration-reabsorption theory was formed in the twenties. According to this theory the relation of glucose as a typical »threshold substance» could be expressed by the equation:

$$\begin{aligned} \text{plasma-sugar (mg\%)} \cdot \text{ultrafiltrate (mlmin.)} &= \\ &= \text{reabsorption (mgmin.)} + \text{glycosuria (mgmin.)} \end{aligned}$$

there being good grounds for the assumption that the glucose diffuses through the glomerular membrane rapidly enough for the same glucose concentration to be established in the ultrafiltrate as in the water phase of the plasma.

Works by Poulsson (22), Ni & Rehberg (20) and Bjering & Iversen (3) marked some progress but, chiefly on account of technical difficulties, did not bring complete clarification. Ni & Rehberg's work was responsible for the hypothesis that a difference in the concentration of glucose in the preurine in the tubules and that in the plasma outside the tubules governed the value of the reabsorption, it being thought that the tubules cells could maintain only a certain maximum difference, an excess of which would involve glycosuria. In 1938 Shannon & Fisher (23) repeated Ni & Rehberg's experiments on *normal dogs*. The glomerular filtration was determined by means of the creatinine clearance and

the plasma-sugar was elevated by intravenous injection of glucose. But whereas Ni & Rehberg experimented with single injections; Shannon & Fisher employed continuous perfusion to keep the plasma-sugar practically constant in each clearance period. It was now observed that at some level above the threshold the reabsorption became quite constant, irrespective of the plasma-sugar, for values between 300 and 1200 mg%. In a subsequent work published in 1941 (24) this was carried still further and the maximum minute quantity reabsorbed was called glucose T_m in analogy with the initials generally employed in American literature for the maximum tubular excretion for doxarast and similar substances (T_{max} = tubular maximal excretory mass).

In man, Goldring, Chasis, Ranges & Smith (9) in principle found the same as Shannon et al. in dogs. T_m for normals was found to be about 340 mg, later 375 mg per minute; corrected to a surface of 1.73 sq. m. it was unchanged for plasma-glucose values from 300 to 700 mg%.

In contrast, we have the experiments of Govaerts & Müller (10) on diabetic dogs, and of Steinitz (27) on man. They did not find the absolute quantity of glucose, but the quantity absorbed from each cubic centimetre of the ultra-filtrate to be a constant. This quantity they call the «maximum threshold», i. e. a concept quite different to the usual threshold, which they term «seuil d'apparition». Thus their results actually support the hypothesis of Ni & Rehberg that the concentration differences determine the value of the reabsorption.

In experiments with seals Hiatt & Hiatt (15) had difficulty in demonstrating a constant maximum reabsorption for glucose; it appears from a diagram, however, that they worked with plasma-glucose concentrations that were too low.

Finally, in tests made on *patients with renal glycosuria* Friedman, Selzer, Sugarman & Sokolow (8) found that it is only at low blood-glucose concentrations that reabsorption is so defective, whereas at higher levels it even exceeds the normal. Judging from these results there is no definite maximum for the reabsorption, and according to their material they found no such maximum in normal subjects either.

Own Experiments.

As technique is all-important in experiments of this kind, I shall first describe mine in detail. All experimental individuals

lay with the catheter in position throughout; at the close of every clearance period the bladder was washed out with 50 ml of water. The diuresis was maintained by giving one or two glasses of water per hour, commencing with two or three glasses (each containing 180—200 ml). The inulin was infused continuously intravenously, and simultaneously as a rule glucose in varying concentrations. Some were also given glucose by the mouth. The first experimental period began at the earliest 45 to 60 minutes after infusion began.

The plasma-glucose was determined in plasma from heparinized venous blood which was immediately centrifuged and corrected for the arteriovenous difference; this difference was found by means of simultaneous samples of freshly flowing ear blood and the whole blood from the vein prior to centrifuging. By letting the person hold his hand in water at 50° for five minutes before the venous puncture the correction will often be made insignificant. The blood-sugar analyses were made by means of the original Hagedorn-Norman-Jensen method. The urine-sugar determinations were made by means of Benedict's macro-method.

The inulin determinations were carried out with a modification of Alving, Rubin & Miller's method (1) after fermentation.

The mean values of inulin and glucose in plasma for the various periods were calculated by interpolation up to 3 minutes before the middle of the period. All analyses were double. Results with more than 5 % difference were discarded. As a rule the difference was under 2 %.

For some of the experimental persons the «sugar threshold» was also determined, the blood sugar (ear blood) being taken every ten minutes at the beginning of the continuous glucose infusion, and the urine fractionated in two-minute periods, whereafter the urine was tested for glucose by Almén's reaction. The change of the reaction was very marked.

Experiments with Normal Persons.

Table 1 A is given as an example of a normal experiment. The main substance of the table is presented graphically in Fig. 2. The injection of inulin and glucose was stopped at the beginning of the last period after which it is very difficult to determine the exact average value owing to the rapid fall of the blood-sugar. Nevertheless, the reabsorption is very constant. It may be objected that the plasma-sugar did not vary enough, especially that it

Table 1.

	Time	Diur- sis (ml per min.)	Inulin clear. (ml per min.)	Plasma glucose (mg%)	Glucose in filtrate (mg per min.)	Glucose in urine (mg per min.)	Tm (mg po min.)
A. Normal fe- male: age: 32 years, .. height 159 cm.. weight 49.6 kg 20.5-44	9.15—9.30	11.8	107.7	218	234.7	+	—
	9.30—9.45	12.1	118.7	267	316.9	33.0	283.9
	9.45—10.00	8.7	112.2	308	345.6	63.4	282.2
	10.00—10.15	5.0	103.4	337	348.5	71.5	277.0
	10.15—10.30	10.0	113.8	345	392.6	100.7	291.9
	10.30—10.45	10.7	110.3	346	381.6	106.6	275.0
	10.45—11.00	6.0	100.0	329	329.0	61.6	267.4
B. normal male age 23 years height 172 cm, weight 61.5 kg 5-4-45	11.16—11.29	17.8	132.0	482	636	302	334
	11.29—11.46	17.1	133.0	486	647	344	303
	11.46—12.01	12.6	133.8	480	642	333	310
	12.39—12.48	20.5	147.0	720	1058	775	283
	12.48—12.58	19.2	145.4	725	1054	773	281
C. Diabetic, female, age 55 years, height 157 cm, weight 65 kg. 15-2-45	11.27—11.50	5.87	92.0	416	383	143	240
	11.50—12.08	6.00	99.0	430	426	183	243
	12.08—12.30	7.97	98.8	474	468	206	262
	12.30—12.51	6.57	95.5	514	491	232	259
	12.51—13.05	10.36	95.0	540	513	305	208
	13.27—13.38	7.27	95.0	614	583	335	248
	13.38—13.52	7.57	97.3	615	598	346	252
D. Diabetic, female, age 54 years, height 150 cm, weight 60.1 kg. 30-6-44	10.20—10.54	4.53	55.5	374	207.6	41.1	166.5
	10.54—11.22	4.38	55.0	454	249.7	74.4	175.3
	11.33—11.53	3.40	58.9	461	271.5	100.8	170.7
	11.53—12.20	3.78	63.6	451	286.8	115.7	171.1
		Aver.	58.25			Aver.	170.9

was not taken up very high. This is difficult with non-diabetics, but in a similar experiment (Table 1, B) it was possible by intravenous injection of 8.5 ml 30 % glucose solution per minute to get the blood-sugar to rise to about 725 mg% without discomfort of any kind. In the three foregoing periods the plasma-sugar lay at about 480 mg%. Having regard to the very high plasma sugar, a difference so small as 34 mg between the Tm determinations at the two plasma-sugar levels cannot signify any real difference, as it corresponds merely to an error of 4—5 ml in determining the ultra-filtrate, a value that lies within the experimental error. Experiments with a third normal person gave a similar result.

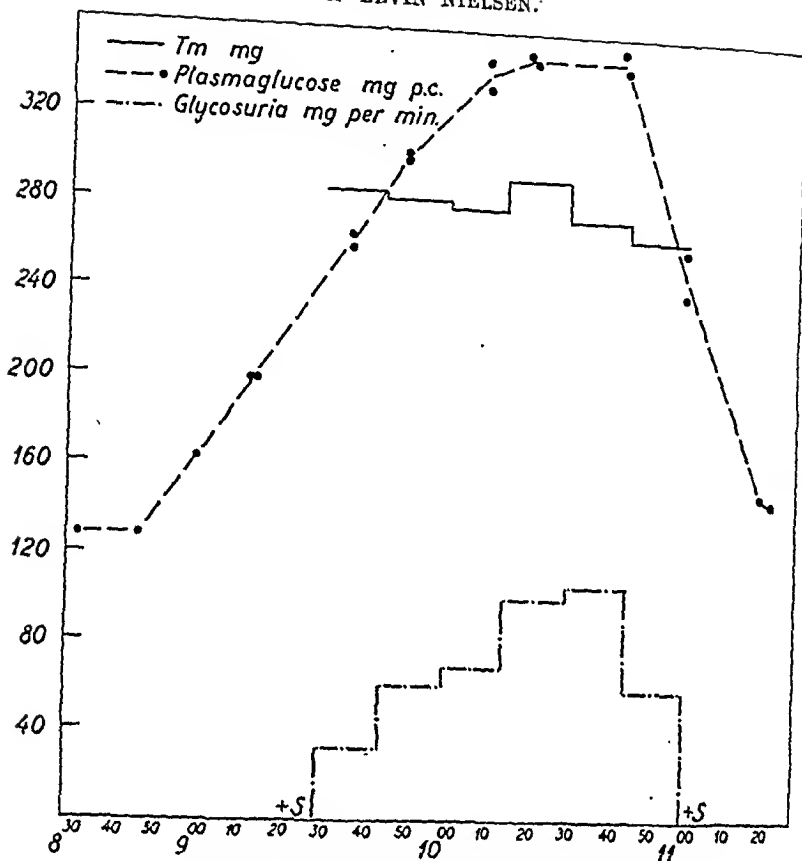


Fig. 2. Experiment Table 1 A, see text.

Experiments with Diabetics.

Tests were made with two diabetics with no known or demonstrable renal affection or any other complication of their diabetes, and three with various complications. It is much easier to obtain stable blood-sugar values with diabetics than with normal individuals, and of course the quantity of glucose to be infused is not nearly so great. On the person Table 1, C the injection of 2.33 ml 20 % glucose intravenously per minute and 70 g glucose by mouth caused a quite steady rise in the blood-sugar in the course of three hours to about 600 mg%, whereafter it remained almost constant for the remainder of the experiment. It will be seen from the table that there is no difference in the reabsorption with the ultrafiltered quantity of glucose at about 400 and about 600 mg. The low value for T_m in the fifth period is probably due to an error in the

urine-sugar determination, which when shown graphically is seen to lie disproportionately high. No insulin was given before the experiments; the usual dose otherwise was 32 + 20 I. U. Insulin Leo Retard, with a full diet without sugar.

Three diabetics had the following complications: 1) benign hypertension, but normal renal function, judging from microscopic tests, urine and inulin clearances. Here the T_m was of the same order as the others. 2) Albuminuria, retinitis, slight cylindruria, normal blood pressure. T_m of the same value. 3) Hypertension (170 mm Hg systolic, 90 diastolic), slight retinitis, normal urine microscopy. This case was regarded as one of incipient nephrosclerosis, the urine clearance being 40 ml (cor. 45 ml) and the inulin clearance 58 ml (see Table 1, D). At the same time the glucose T_m was 171 mg. On calculating the line threshold by dividing the T_m by the inulin clearance it is seen to be very high, 293 mg% plasma sugar, or at a rough estimate 270 mg% blood-sugar. The directly determined threshold lay between 240 and 260 mg%.

I was able to make a sufficiently exact determination of the sugar threshold for five experimental persons. For four it was 10–15 % below the line threshold, for the fifth it was 26 %.

Finally, I tested a patient with renal diabetes. In the first test T_m was found to be 56, 34, 21, 15 and 26 mg, the average thus being 30 mg. At a second attempt the tests were made at widely different blood-sugar levels, but this did not give much difference in the T_m (see fig. 3). In fig. 3 the ultra-filtrated quantity of glucose is plotted along an oblique line on the scale of the ordinate. Vertically below each point is the corresponding quantity of urine-sugar. The lower oblique line is drawn approximately through the urine-sugar values. The distance between the two lines indicates the T_m . The marked fluctuations in the value of T_m should not be considered in relation to the T_m itself, it being so small, but should be seen in relation to the ultrafiltrated quantity of glucose and the glycosuria. According to the diagram it is quite evident that the excretion of urine-sugar runs closely parallel to the quantity of ultrafiltrated glucose, regardless of the latter's value; in other words, the reabsorption is constant.

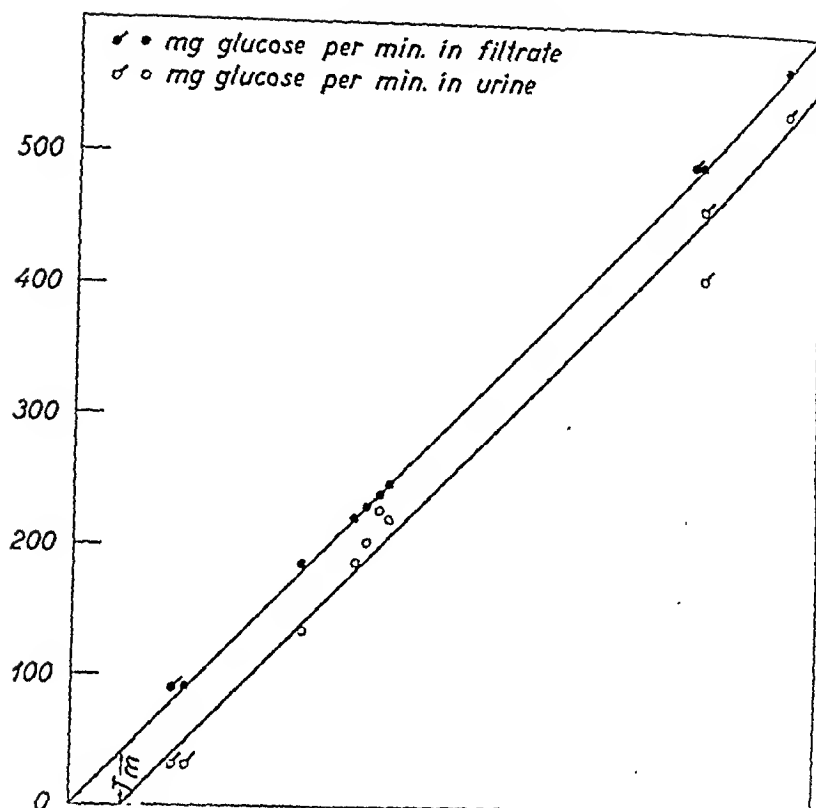


Fig. 3. T_m -determination for patient with renal glycosuria.

Discussion.

Originally this work was carried out without knowledge of the recent American investigations on the subject. As these investigations cannot be said to agree mutually, I decided to publish the present work, stimulated additionally by Ekehorn's results (4). The whole material is shown in Table 2.

a) T_m . It would appear from Table 1 that the reabsorption of glucose in the experimental periods is very constant from one period to another, even though the ultrafiltrated quantity of glucose fluctuates very considerably on account of the blood-sugar fluctuations. On this point there is apparently no fundamental difference between normals and diabetics with sound kidneys. For a diabetic with a much reduced ultrafiltration the values for T_m are very constant, and, as anticipated, a direct

Table 2.

Glucose Tm, inulin clearance of normal individuals, diabetics and one case of renal diabetes.

	Sex	Age	Inulin clearance (ml per minute)	Glucose Tm (mg per minute)
			(corrected to 1.73 sq. m.)	
<i>Normals</i>	M	23	140	275
	M	25	140	302
	F	33	128	326
<i>Diabetics</i>				
0 complications	M	20	122	254
	F	54	101	252
Diab. + hypert.	F	69	122	313
Diab. + albumin.	F	41	128	300
Diab. + incip. nephroscl.	F	54	65	192
Renal diabetes	F	47	90	ca. 45

determination of the «sugar threshold» reveals a high threshold, approximately about 10 % below the line threshold when the latter is converted to blood-sugar.

b) *The threshold concept.* Various forms of «threshold» are referred to in this work: 1) The original one (Cl. Bernard), where the threshold is the blood-sugar concentration at which the urine changes from minimum quantities of glucose not demonstrable with ordinary reagents to a considerable content. This is usually called «the threshold on ascending blood-sugar curves» in contrast to «the threshold on falling curves», where the urine changes from having a sugar content to being sugar-free. This differentiation is made because of the general assumption that the threshold is lower on falling than on rising curves. 2) The form of threshold which Govaerts & Müller (10) call «seuil maximal» refers exclusively to the sugar content of the urine and therefore has nothing in common with the original use of the word threshold, which meant the glucose concentration in the *blood*. 3) Finally, the term «line threshold» is employed several times. It is determined by finding the point of intersection between the straight line which in an coordinate system characterizes the relation between urine-sugar and blood-sugar some distance above the threshold, and the abscissa. One arrives at the same numerical value by dividing the maximum tubular reabsorption by the average ultrafiltration,

i. e. $\frac{T_m}{\text{in. cl.}}$, if we disregard the difference between the glucose concentration in plasma and that in whole blood.

As according to the above equation for the excretion of a threshold substance it is the quantity of ultrafiltrated glucose which, together with the reabsorption, will decide the onset and extent of glycosuria, it is impossible to lay down any blood-sugar value at which glycosuria will always occur in a certain individual; for this would presuppose partly that the ultrafiltration is always constant, which it is not, as is clear when one measures the inulin clearance, and partly that the distance between the »threshold» and the line threshold is also constant. In other words, we must admit that as far as glucose is concerned, the term »threshold» can no longer be maintained as a special physiological characteristic of the work of the kidney, as the height of the blood-sugar at the onset of glycosuria must vary according to the proportion between the two values which in this connection are active, namely the ultrafiltration and the reabsorption. On the other hand, in the daily clinical work it will still be useful to speak of diabetics with a »high» or a »low» sugar threshold.

c) *The distance between threshold and line threshold.* In the five cases where the determination of the threshold was more exact it proved to be 10—15 % below the calculated line threshold, in one instance 26 % below. As the threshold will depend upon when the first tubules will allow some glucose to pass, this in other words may give us an impression of how uniformly the glomerular function of the various nephrons is regulated vis-à-vis the tubular function. If the threshold lies only 10 % below the line threshold, it must mean that the first tubules only became overwhelmed with glucose at a time when 90 % of the total tubular function is already in use, for the glucose content of the plasma must be assumed to be the same in all glomeruli. Accordingly, between the various nephrons there must be a remarkably slight distribution of the inner harmony between the glomerular and the tubular functions. This aspect of the matter is discussed at greater length by Smith et al. (25).

d) *The quantitative limitation of the reabsorption.* Kalckar's investigations (18) seem to establish that the reabsorption of glucose is the result of specific phosphoryling-dephosphoryling processes in the tubules. Ni & Rehberg (20) considered that differences between the urine in tubules and the plasma outside the tu-

ules limited the value of the reabsorption. The present experiments with normals and diabetics with a normal renal function gave no clear answer to the question. On the other hand, the appearance of the high line threshold for the patient with the greatly reduced inulin clearance seems to suggest that the concentration differences cannot be the factor that decides the value of the reabsorption; for these defective kidney prove capable without glycosuria of maintaining larger concentration differences than we observe in normal kidneys. The cause of the appearance of this greater difference in concentration must lie in the fact that although the reabsorption is lower than normal, the glomerular function, measured by the ultrafiltrate, is relatively still more reduced, so that the ultrafiltrate may contain a higher concentration of glucose than normally before reabsorption fails.

c) *The rising threshold of elderly diabetics.* If many diabetics develop a somewhat higher threshold with age, the reason must undoubtedly lie mainly in the more reduced glomerular function as a result of arteriosclerosis in relation to the tubular function (see above). A higher sugar threshold in nephritis was already demonstrated in 1917 by Hamman & Hirschman (13).

f) *Ekchorn's criticism of Tm.* In a publication from 1943 Smith (25) states that the inulin clearance of normal males is about 136 ml per minute, the glucose Tm about 375 mg, and for females 115 ml and 303 mg respectively. Whereas my figures for inulin clearance are of the same order, those for glucose Tm are somewhat lower, but owing to the smallness of the material no vital significance can be attached to them. In his work Ekchorn (4) is very critical of such high values for the glucose Tm, on the grounds that these would involve much higher figures for the sugar threshold than are usually regarded as normal (170—180 mg%). It is true that the calculation of the line threshold gives a very high value, e. g. $375 : 136 = 2.76 \text{ mg\%}$; but in the first place, Ekchorn overlooks the fact that it is a question of plasma-sugar, which at higher values lies 5—15 % above the blood-sugar; and in the second place, the calculation gives the line threshold, not the usual sugar threshold, which lies 10—33 % lower. If the present example is corrected 10 % for the difference of plasma-sugar from blood-sugar, and then 25 % for the difference between the two kinds of threshold, we arrive at a sugar threshold of 189 mg%, which seems to be very acceptable.

g) *Inulin clearance-ultrafiltration.* My experiments show, though

indirectly, that under the given circumstances the inulin clearance must lie very near to the actual ultrafiltration. If we imagine a systematic deviation in a positive or a negative direction, it would at the higher plasma-sugar values make the calculated reabsorption of glucose too high or too low, so that it would not be possible to find it fairly constant unless there was an equally marked deviation in the reabsorption in the opposite direction, a deviation which also varied with the variations in the plasma-sugar. This, however, seems very improbable.

h) *Explanation of fig. 1.* Thus, in three normals, five diabetics and one person with renal glycosuria it is shown that there is a fixed upper limit for the reabsorption of glucose, regardless of fluctuations in the quantity of the ultrafiltrate, the glucose content and the diuresis. This being accepted, it is also clear that the rectilinear relation of the very first figure between blood-sugar and urine-sugar is fully applicable only when the ultrafiltration is constant, as was earlier shown by Bjering & Iversen.

Summary.

After reviewing the literature the author describes his experiments on determining the maximum renal reabsorption of glucose in three normal persons, five diabetics and one renal diabetic. For each of them it was possible to demonstrate an individual upper limit of reabsorption, that was very constant during the tests, that for normals lying at about 300 mg per minute. The author explains the difference between the usual sugar threshold and the line threshold. It is also explained how defective kidneys can develop a high sugar threshold and how the distance between the sugar threshold and the line threshold can be utilized for judging how well the glomerular and tubular functions are harmonized with regard to glucose.

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The Inhibitory Effect of the Oxygen Pressure in Blood on Respiration through the Intermediacy of Chemo-Receptors.

By

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Introduction.

The important investigations of Haldane (19) have shown that the chemical regulation of respiration depends for a great part on the stimulating effect of carbondioxide on the respiratory centre.

After 1930 many articles appeared which threw quite a new light on this regulation. It had appeared that also lack of oxygen influenced breathing. A hyperventilation was produced and this is almost unanimously explained in the literature by assuming that lack of oxygen as such has a stimulating effect. This stimulus is said not to act directly on the respiratory centre but on the chemo-receptors in sinus caroticus and aorta. It is generally accepted that the desaturation normally present in arterial blood is already a stimulus, and that when this desaturation increases the stimulus becomes correspondingly greater.

I have never been able to agree with this explanation and believe rather that the specific effect of oxygen is an inhibitory one.

In Chapter I I shall discuss the influence of the lung-ventilation on the quantum of oxygen and carbondioxide in alveolar air and arterial blood.

It is pointed out that the term »normal desaturation» may be misunderstood, also that an increase or decrease of lung-ventilation decreases or increases respectively the quantity of carbondioxide in arterial blood.

OXYGEN PRESSURE IN BLOOD.

Chapter II gives a short survey of the literature with regard to the chemo-receptors.

Chapter III gives the results furnished us by clinical observation when patients are treated continuously with oxygen for a considerable time. These results support our opinion regarding the inhibitory effect of oxygen on respiration.

In Chapter IV we shall consider the actual value of the explanation given up till the present, while in Chapter V our own opinions on the subject are stated.

Chapter I.

As is known, the renewing of air in the alveoli does not take place by currents, but principally by diffusion.

Wiggers (40) calculates the air in the lungs that is renewed at every respiration to be about $12\frac{1}{2}\%$.

Dry atmospheric air is composed of:

20.94 % O_2 ; 0.03 % CO_2 and 79 % N_2 .

On an average we find for the composition of alveolar air:

14.5 % O_2 ; 5.1 % CO_2 and 79 % N_2 .

Thus the percentage of nitrogen in alveolar air is the same as that in atmospheric air, that of carbondioxide and oxygen is respectively higher and lower.

When, however, the respiration is voluntarily increased, by which the renewing of the air is improved, the oxygen pressure in the alveoli also increases. Houston (27) showed this also experimentally.

When he brought about an anoxemia in test persons, a voluntary increase of the respiratory minute volume produced a distinct increase of arterial saturation.

When the barometric pressure is 760 mm, the partial pressure of oxygen in the atmospheric air is $\frac{20.94}{100} \times 760$ is approximately 160 mm Hg. For the calculation of the alveolar oxygen pressure the pressure of the saturated water vapour at body temperature must be subtracted. Then we find for it $\frac{14.5}{100} \times (760$

— 47) is approximately 100 mm Hg. The pressure of oxygen in blood-plasma will also amount to approximately 100 mm.

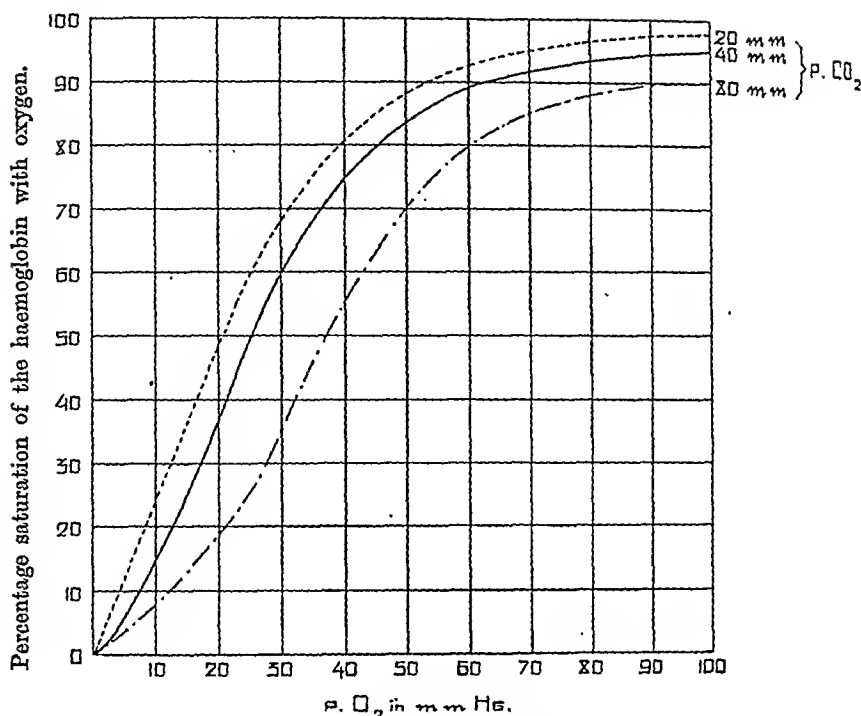


Fig. 1. Dissociation curve of oxyhaemoglobin (by Henderson).

Figure 1 shows the saturation of haemoglobin at different pressures of oxygen. When the carbondioxide pressure is higher, the curve shifts to the right and vice versa.

If arterial puncture is carried out in healthy persons and the blood so obtained is analysed for its oxygen content, it appears that the haemoglobin is not totally saturated, but only for 95 %. Under normal conditions a slight desaturation of 5 % would appear to exist.

Various investigators explain this desaturation as follows.

During the respiratory movements the different parts of the lung are not all equally ventilated. In the well-ventilated parts the blood cannot take up more than 100 % oxygen; in the less-ventilated parts perhaps only 90 %. The result is that in the vena pulmonalis mixed blood is found that is saturated for 95 %. From this we may conclude that, in normal respiration, the action of the lung to provide the blood with oxygen is not quite ideal. In other words, there is something wrong in the behaviour of the organism. Under normal conditions there is indeed a desaturation of 5 %.

In my opinion the explanation given is superfluous, and therefore erroneous. The saturation of blood is determined as follows: the quantity of oxygen in arterial blood is determined (a cc.). After that the blood is shaken with air to saturate it completely, and the quantity of oxygen in this blood is determined (b cc.).

The saturation is then $\frac{a}{b} \times 100 = 95\%$. This 5 % desaturation, however, points by no means to a less good functioning of the lung. Indeed these two quantities of chemically bound oxygen may not be compared, because they have been obtained under different circumstances. Only when a desaturation might be found if, in the alveolus, the blood has been in contact with air of which the oxygen percentage was 20.94, the barometric pressure need not be decreased by 47 mm and there was not at the same time a carbondioxide pressure of 40 mm, only then might we conclude to a less good functioning of the lungs as regards the saturation of blood with oxygen. In normal circumstances it is impossible for the blood to take up more oxygen than it does in fact. What it can take up more of oxygen in special circumstances is undoubtedly important from a chemical point of view, but we must hold to the fact that in the lung-alveolus the oxygen pressure amounts to 100 mm, and that at this pressure the haemoglobin takes up a definite quantity of oxygen. With respect to atmospheric air the saturation is actually only 95 %. In other words, with respect to atmospheric air, there is indeed a desaturation of 5 %.

It has been an open question what may really be the stimulus for the respiratory centre. On this point there were principally two theories. According to one, the specific stimulus is carbon-dioxide, according to the other, the changes in the pH of the blood. Haldane (19) decided the question at issue by furnishing the proof that carbondioxide was the specific stimulus. If the carbondioxide percentage in the alveolus is raised, there is also an increase in respiration, principally by augmenting its depth. If the carbondioxide percentage in the alveolus be decreased, for instance by hyperventilation, a decrease in respiration follows. At the same time Haldane pointed out that not the carbon-dioxide percentage was of importance but the partial carbon-dioxide pressure. At barometric pressures varying from 300 to 3 000 mm Hg the alveolar carbondioxide pressure remained almost constant at approximately 40 mm, and the body tries to

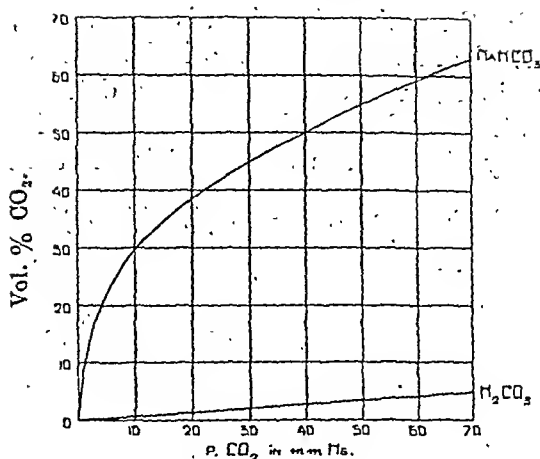


Fig. 2. Carbon dioxide dissociation curve (by Barcroft).

maintain this pressure in all circumstances. In hyperventilation when carbon dioxide is washed out, the pressure is lowered in the lung-alveolus and thereby also in the blood-plasma. This pressure then falls below the level at which the respiratory centre is still stimulated. When experimenting at great heights Haldane observed that when the barometric pressure was lowered respiration increased. He puts this down to oxygen deficiency in the blood. This lack of oxygen is said to render the respiration-centre more sensitive to carbon dioxide, causing respiration to increase. That the respiration centre becomes more sensitive is assumed to be one of the means of compensation of the body. For by the increased pulmonary ventilation the air in the lungs is better renewed, whereby the blood also takes up more oxygen. If the pressure of oxygen decreased still more, the breathing became shallow, irregular and stopped altogether. The respiration centre being hypersensitive it gets overfatigued and fails.

When there is oxygen deficiency a hyperventilation occurs. Owing to this the carbon dioxide is, as it were, washed out, and in consequence, we get a primary low carbon dioxide percentage in the lungs. In other words: the carbon dioxide pressure in the plasma will also become lower. In the ratio $\text{H}_2\text{CO}_3/\text{NaHCO}_3$ the numerator becomes smaller and the reaction of the blood shifts to the alkaline side. To obviate any great changes in the pH, the denominator of the ratio must also become smaller. From the dissociation curve of NaHCO_3 given in figure 2, it appears that when we lower the partial pressure of carbon dioxide, whereby

the points on the line of H_2CO_3 shift to the left, the quantity of NaHCO_3 will also decrease. Then a low alkaline reserve will be found, in this case indicating an acidosis. On the other hand when the outlet of carbondioxide in the lungs is impeded, for instance in decreased pulmonary ventilation, the percentage of carbondioxide in alveolar air, and therefore in the plasma, will rise. The NaHCO_3 will then rise too, so that pH will remain constant again, and a higher alkaline reserve will be found, indicative of an acidosis.

Starting from the alkaline reserve, as is usual in clinics, we must, in order to explain the values found, bear the following in mind. When there is a low alkaline reserve, this generally indicates an acidosis. With a coma diabeticum for instance, in which a great many acids are formed, these acids are neutralized by the NaHCO_3 . We find then a direct decrease of NaHCO_3 and, consequently, a low alkaline reserve. It is also possible, however, that the decrease of NaHCO_3 is caused indirectly, when by hyperventilation great quantities of carbondioxide are washed out the quantity of H_2CO_3 in the ratio is reduced. From the dissociation curve of NaHCO_3 it then appears that, as a consequence, the quantity of NaHCO_3 also becomes lower. In this case, too, we shall find a low alkaline reserve indicating an alkalosis.

On a former occasion (38) we gave the following schema:

Blood	Cause	Result	Alveolar air	
Low alkaline reserve	<i>c. g.</i> coma diabeticum.	Acidosis (non-gaseous)	Secondary	Low CO_2
	<i>c. g.</i> hyperventilation.	Alkalosis (gaseous)	Primary	
High alkaline reserve.	<i>c. g.</i> alkaline doses.	Alkalosis (non-gaseous)	Secondary	High CO_2
	<i>c. g.</i> omphysema	Acidosis (gaseous)	Primary	

As in the clinic the term «alkaline reserve» is much used it is put first in the schema. From a physiological point of view, or rather, in connection with changes in respiration, that is, changes in the percentage of alveolar carbondioxide, this schema can better be read from right to left. When in alveolar air a primary low

carbondioxide percentage is found, this will in the end agree with a low alkaline reserve in the blood. If, on the contrary, this percentage in the lung alveolus is higher, a high alkaline reserve will be found in the blood too. This explanation is given in order to refer to it later on in this article.

As was said above, Haldane explains the increase of respiration in the case of oxygen deficiency, by assuming in these circumstances changes in the respiratory centre, rendering it more sensitive to carbondioxide. This would result in an increase in respiration.

From a logical point of view there is nothing against this explanation. For the increase of respiration is explained by the activity of the carbondioxide actually present in the blood, which in the case of oxygen deficiency can act relatively stronger on the more sensitive respiratory centre. In reality, however, it was seen that this possible process was not realized in nature.

For it has appeared that the sinus caroticus plays a great part in the regulation of respiration. The lack of oxygen is held to have no direct effect on the respiratory centre, but to stimulate respiration by reflexes from this sinus.

Chapter II.

In the historical survey published by Gemmill and Reeves (16), and by Cordier and Heymans (10) in 1933 and 1935 respectively, we find the following.

As early as 1882 Rosenthal pointed out that oxygen deficiency had a stimulating effect on respiration. Pflüger (1868) explained the increase in respiration by assuming that when there was lack of oxygen certain metabolic products resulted, which stimulated the respiratory centre. Hermano opined that when there was oxygen deficiency the respiratory centre became more sensitive to carbondioxide. Gesell (1923) held that during an anoxemia pH-changes in the respiratory centre occurred. In 1927 the histological studies of de Castro appeared, in which it was suggested that the nerve-endings in the adventitia of the sinus are responsible for the presso-reflexes, whereas those of the carotis body would be sensitive to chemical changes in the blood.

In Fig. 3 we give a sketch of the branches of the carotis, as illustrated in an article of Heymans (23). The nerve-endings that are said to be sensitive to pressure-changes are situated in the

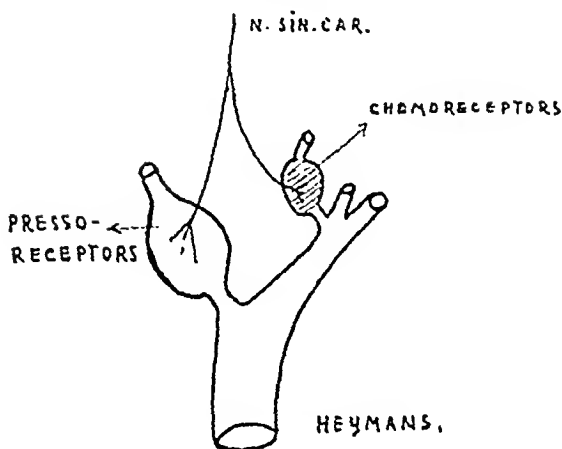


Fig. 3.

vascular wall, mainly in a dilatation of the arteria carotis interna. They are called presso-receptors. The nerve-endings that are sensitive to chemical substances, are found in the glomus caroticum. They are called chemo-receptors. They are also found in the aorta-tissue. The influence of the latter, however, according to Ger-nandt (17) is not so great as that of the sinus. They are supposed to be groups of cells of a paraganglionic character, partly sympathetic, partly parasympathetic.

We shall here give our attention principally to the influence of oxygen and carbondioxide on the regulation of respiration. This influence is ascribed, for a great part at least, to the activity of these chemo-receptors of sinus and aorta.

Heymans especially, has demonstrated these reflexes empirically. In his publication of 1930 he described experiments on dogs, the sinus of which he perfused with blood by means of a pump. The innervation of the sinus was intact. He also took crossed circulation experiments, in which the sinus of dog B was perfused with blood of dog A. In this the innervation of the sinus of dog B remained intact. The conclusions drawn from these experiments as bearing upon our subject are, in short, increase of carbondioxide and anoxemia cause reflexly a stimulus of respiration. After cutting the sinus nerve increase of carbondioxide and lack of oxygen had no further influence. This reflexogenous

regulation even predominates over the sensitivity of the respiratory centre.

In the course of time several other investigators, among others, Schmidt (34), Gemmill and Reeves (16), Wright (41), Smyth (36), Bouckaert and Pannier (5), Bernthal (3), have been able to confirm these discoveries, in the main at least.

The suggestion that the regulation by reflexes predominates, has been much criticized. Especially Schmidt (34; 9; 35) and Gollwitzer-Meyer (18) opposed it. They held that the direct effect of carbondioxide on the respiratory centre was much greater. The reaction of the chemo-receptors would be quicker. According to Schmidt the stimulus of the respiration takes place as follows:

1. by carbondioxide direct on the respiratory centre.
2. by oxygen deficiency by reflexes.

During normal respiration the regulating activity of the sinus carotieus would be of no importance, it being only an accessory mechanism (9). But it was of importance during anoxemia. Hilding Bjurstedt (25) even presupposes that during a serious anoxemia there is no central regulation by carbondioxide at all; an alkalosis is caused by the strong hyperventilation as the carbondioxide is being washed out. Lung ventilation could then be maintained only by the stimulus of oxygen deficiency acting solely by reflex.

Heymans, however, held to his opinion. In 1939 he published an article in cooperation with Bouckaert (23) from which it appeared that he maintained his point of view. Euler and Liljestrand (12) asserted that also under normal conditions the sinus carotieus emits a continuous slight stimulus, because normally there is always a slight desaturation in arterial blood. The decrease of respiration which was found after inhaling oxygen was explained by Marshall (32), Euler and Liljestrand (13), Watt (37) and Heyneman (24) as follows: normally there is always a slight stimulus via the chemo-receptors. If by inhaling oxygen the normal desaturation is eliminated, this extra stimulus will be removed and respiration decrease.

The above experiments were performed on anaesthetized animals. In my opinion the experiments by Gemmill (15), Jongbloed (29) and Dautrebande (11) must be mentioned separately, because they experimented on animals that were not anaesthetized. They observed that also after denervation the oxygen deficiency caused a hyperpnea, in contrast to all other investigations on anaesthe-

tized animals, whereby after denervation oxygen deficiency had scarcely any effect. This would point to the fact that the lack of oxygen also influenced the centre, but that this centre was put out of action by the narcose.

It is true that Jongbloed explained the hyperventilation caused by lack of oxygen after denervation, by assuming that the nerves of the chemo-receptors had recovered. This, however, is rendered improbable by the experiments of Dautrebande, which were published a year later. This author also saw that oxygen deficiency in animals that had been denervated beforehand caused a hyperpnea. This hyperpnea disappeared, however, when the animals were anaesthetized afterwards. If the nerves of the chemo-receptors should have recovered, the hyperpnea must have remained, for in all experiments on anaesthetized animals with intact sinus mechanism, that were exposed to oxygen deficiency, they reacted by a hyperpnea. The conclusion seems to be justified that not only carbondioxide stimulates the respiratory centre, but also oxygen deficiency.

The only experiments that are incompatible with this, as far as we know, are those of Watt in 1943 (37), who found a depression in the respiration in non-anaesthetized dogs during a slight anoxemia after denervation.

The study of the literature on this subject gives rise to the following observations.

1. From this it appears with certainty that the chemo-receptors influence the regulation of respiration, and that all investigators without any exception explain this regulation by accepting the lack of oxygen to be such as to have a stimulative effect on the chemo-receptors.

2. If we eliminate the chemo-receptors, we remove the influence exercised by the lack of oxygen on respiration by reflexes. It should not be forgotten, however, that then we also eliminate the stimulating influence of carbondioxide, so that we may not ascribe the phenomena exclusively to the absence of the effect oxygen may have.

3. When in experiments the animals were made to inhale carbondioxide with the aim of investigating the stimulating effect of it on respiration by reflexes, the investigators often used carbondioxide in oxygen, *e. g.* 5 %—10 % carbondioxide in oxygen (10). The oxygen was added to eliminate the slight desaturation that normally occurs, that the experiments should not be impeded

by the stimulating effect of it. In the course of this article it will appear that, in my opinion at least, the results of these experiments would be better justified if gas-mixtures had been used with, at least the normal percentage of oxygen so that the increase of carbondioxide percentage would involve an equal decrease of nitrogen, as the latter, as far as is known, does not influence respiration.

4. When perusing the articles on this subject, we are struck that the writers have been content to mention the decrease of respiration after breathing oxygen, to demonstrate in this way that the stimulus of oxygen deficiency on chemo-receptors was removed. We get a strong impression, however, that breathing oxygen had more far-reaching consequences. This is probably what Marshall (32) meant, when he pointed to the incongruity between the decreased lung ventilation after breathing oxygen and the previous anoxemia. When a certain degree of desaturation resulted in increase of respiration of *e. g.* 10 %, it appeared that on inhaling oxygen this increase of 10 % not only disappeared but respiration decreased still more.

Chapter III.

If we consider what data the clinical observation supplies when patients with anoxemia are treated for a considerable time in high oxygen atmospheres (an oxygen-tent), we can summarize them in this way:

1. An anoxemia in consequence of decreased lung-function always disappeared. In eleven patients in whom we determined the oxygen- and carbondioxide-content in arterial blood during treatment in the oxygen-tent, it appeared that even desaturations of 30 % were entirely relieved (38). This had the important result that all serious symptoms attributable to anoxemia disappeared.

2. It is known that in anoxemia a rise of haemoglobin percentage is observed. When patients are treated continuously with oxygen, a fall in the haemoglobin percentage was generally seen. This fall was often slight, and sometimes only one or two percent, even after a nine days' uninterrupted treatment. In some cases even a rise was observed.

The rise and fall of haemoglobin percentage when the oxygen pressure was diminished or augmented might be the result of changes in blood-volume, the capillary wall becoming more or

less permeable by liquids and plasmaproteins. I refer here to statements by Landis (31), Asmussen (1), Hitzengerber (26) and Jongbloed (28). Later on we may have an opportunity to return to this.

3. Of more importance to our subject are the changes that are found in the amount of carbondioxide in arterial blood. This is mentioned by Campbell (6), Katz (30), Richards (33), Barach (2) and Watt (37).

Various explanations are given of the increase of carbondioxide content. On account of the better oxygenation the quantity of lactic acid in blood was supposed to decrease, by which respiration would be less stimulated and carbondioxide retained.

The retardation in the blood-flow was also held responsible for it.

A third explanation was, that on account of the great quantity of oxygen in the blood, the haemoglobin returning to the lung after flowing through the tissues, was for the greater part still saturated. As the reduced haemoglobin undertakes the transport of carbondioxide to a large extent, and this means of transport is removed, the result is an accumulation of carbondioxide in the tissues.

Be this as it may, a considerable increase in the quantity of carbondioxide is found in arterial as well as in venous blood. In their book on oxygen and carbondioxide therapy, Campbell and Poulton (8) describe various cases in which carbondioxide percentage in arterial blood rose materially in one case even to 132 vol. %. This enormous quantity cannot possibly be explained by a quantity of base liberated by oxidation of lactic acid. We, too, invariably found an increase in the arterial carbondioxide percentage, sometimes of 15 vol. % (38).

The increase is readily understood, because by inhaling oxygen the stimulus of the anoxemia ceases, respiration becomes more quiet, and less carbondioxide is washed out.

This increase in percentage, however, is not in proportion to the removal of the stimulus which oxygen deficiency is supposed to have.

These data, too, lead to the same conclusion as in Chapter II sub. 4, namely the increased oxygen-pressure does more than merely remove a stimulus.

Chapter IV.

When we consider the explanation of the stimulation of respiration by lack of oxygen via the chemo-receptors from a logical point of view, we come in my opinion, to the conclusion that this is no real explanation, because it does not elucidate the problem of regulation at all.

The point of view held until now comes in short to this. In anoxemia an increase of respiration is seen. If oxygen is administered this extra stimulus disappears. Normally there is always a slight desaturation. This will continue stimulating the respiratory centre. The stimulation originates in the chemo-receptors, which appear to be sensitive to lack of oxygen.

Let us consider this theory more closely. As was said in the introduction to this article, it is usual to speak of a normal desaturation of 5 %. In my opinion it would be better to speak of an equivalent saturation of 95 %, indicating on the one hand that the quantity of oxygen found is in proportion to the conditions in the lung-alveolus; on the other hand that this quantity can be augmented under special circumstances. If one would to continue speaking of a normal desaturation it must not be forgotten that this is a negative idea, which means nothing less than the negation of the presence of oxygen. Of course it is impossible that something that is not present can act on another thing. Oxygen that is not present cannot possibly be a stimulus for chemo-receptors. The misunderstanding arose because »normal desaturation» (which was accorded even a quantity of 5 %) acquired a positive content.

And yet the experiments showed that when this desaturation increased, respiration increased and when this desaturation ceased, respiration decreased. After the above, it is not necessary to demonstrate that only the oxygen that is present can exert an effect on the chemo-receptors. If this be true it may, even a priori, be expected that a decrease or increase will also bring a change in the respiration.

If a decrease of the oxygen present results in a stimulus of respiration, the qualitative influence of oxygen might be an inhibitory one.

Chapter V.

We can now proceed from the following data:

- I. Decrease in the quantity of oxygen in blood causes an increase in respiration.
- II. Administration of oxygen decreases respiration.
- III. Elimination of the chemo-receptors annuls this effect of oxygen-increase and decrease in anaesthetized animals.
- IV. In unanaesthetized animals elimination of chemo-receptors has much less effect on the changes in the respiration so that, to a certain extent, we may even speak of a reaction to oxygen deficiency as with normal animals.
- V. Breathing oxygen increases the carbondioxide percentage in arterial blood considerably, so that here, too, an incongruity exists between the increase of carbondioxide and the removal of the stimulating effect of oxygen deficiency.

In each of the three preceding chapters it appeared that there was reason to doubt the correctness of the current explanation that lack of oxygen has a stimulating effect on respiration.

Naturally it is not doubt of what the experiments have shown to be facts, namely, that the chemo-receptors activity by reflexes was of great importance for respiration, but doubt whether the cause of this activity is the lack of oxygen.

We shall therefore endeavour to form a hypothesis which will give a good explanation of the subjects treated in the preceding chapters and which is exclusively based on what has been shown in nature to be reality.

When we accept the specific activity of oxygen on the chemo-receptors to be an inhibitory one, we shall see that all phenomena found hitherto can be explained satisfactorily. Our representation of the chemical regulation of respiration by oxygen and carbondioxide is as follows:

- A. Direct effect on the respiratory centre:
 - a. Carbondioxide — stimulating,
 - b. Oxygen — inhibitory.
- B. Indirect effect via the chemo-receptors:
 - a. Carbondioxide — stimulating,
 - b. Oxygen — inhibitory.

Respiration will be regulated by a continuous stimulus on the one hand and a continuous inhibition on the other. This inhibitory activity may change in intensity in proportion as the oxygen pressure in the plasma increases or decreases.

One may ask if there is any real difference when we speak of the stimulating effect of oxygen deficiency or of an inhibitory effect of oxygen on respiration. Indeed they are two ways of saying the same thing. In one way we say it negatively, in the other positively.

If it were merely a difference in the mode of expression but that we formed the same idea of regulation, there would be little against continuing to speak of normal desaturation and a stimulating effect of oxygen deficiency. From the literature, however, we received a definite impression that the effect of oxygen deficiency is held to be positive.

1. »It is interesting that the lack of a chemical substance stimulates nerve-endings into action.» (16).

2. »If the oxygen depression consists essentially in removing some stimulus to respiration it is reasonable that this stimulus is anoxemia.» (32).

3. When there is a serious lack of oxygen the respiratory centre would even be quite eliminated and the only stimulus to respiration is then the said oxygen-lack (via the chemo-receptors). (25).

4. Some believe that the sinus caroticus is merely an accessory mechanism from which stimuli only originate when there is lack of oxygen. (9).

5. Carbondioxide is administered in as much as 90 to 95 % oxygen, and that only to obviate the stimulating effect of the normal, very slight, desaturation. If it were supposed that oxygen as such exerted an effect on the chemo-receptors, such a high oxygen percentage would never have been given in these experiments.

6. Among the different substances with stimulative effect on respiration (by way of the receptors) anoxemia is mentioned together with several chemical substances.

7. How must it be indicated if the oxygen pressure in the plasma is considerably higher than normally? The indication would have to be twice negative. The remark has been made, however, that there is a discrepancy between the decrease of respiration and the anoxemia present at first.

8. Why is an explanation looked for of the fact that the carbondioxide content in arterial blood rises so markedly when patients are treated in high oxygen milieu?

In this way many examples might be cited from which it appears distinctly that only lack of oxygen by itself is mentioned as a stimulus to the chemo-receptors. Therefore we do not intend only to express positively what was formerly said negatively, but also to draw attention to the fact that an increasing pressure also increases this effect proportionately.

Under normal circumstances the carbondioxide pressure of 40 mm forms the stimulus, the oxygen pressure of 100 mm the inhibitory factor. Stimulus and inhibition are balanced. It is known that when carbondioxide pressure is increased an increased respiration occurs, and when carbondioxide pressure decreased a decreased respiration follows.

If oxygen pressure decreases, which means that the intensity of inhibition decreases there is no longer any balance and the stimulus of carbondioxide will predominate, resulting in an increase in respiration. On account of this increase in respiration carbondioxide will be washed out. Its pressure will fall so much that stimulus and inhibitory activity are well-balanced again. This balance will be on a lower level.

But if the oxygen pressure increases, however, the inhibitory activity will become greater, and decreased lung-ventilation will be the result.

This renders it directly unnecessary that the desaturation normally present should be a constant stimulus to respiration.

When we increase lung-ventilation at will, great quantities of carbondioxide can be washed out while because of better renewal of the air in the lungs oxygen pressure in the plasma increases. The consequence may be that the stimulus greatly decreases and inhibition still increases, which results in apnea. We could then no longer speak of apnea due to carbondioxide deficiency (because the carbondioxide pressure comes to lie below the threshold index at which the respiratory centre is only just stimulated) but of an oxygen-apnea: the inhibitory influence of the oxygen predominates the stimulus of carbondioxide. Then the hypothesis of the threshold value of sensitivity of the respiratory centre can be relinquished. During the apnea the oxygen pressure falls and the carbondioxide pressure rises. The inhibition decreases and the

stimulus increases. The carbondioxide pressure may rise so much that it is just stronger than the inhibition. The result will be that respiration starts again, but the regulation will be on a much lower level. If there are more respiratory movements the oxygen pressure will rise again rapidly for the carbondioxide pressure decreases again and had not yet reached the original level. Again a cessation of breathing occurs. Alternately inhibition and stimulus will prevail and the equilibrium will come with increasing rapidity to lie on an ever higher level, till the limits are reached and the normal equilibrium is redressed.

Since it is of importance for the organism that the carbon-dioxide produced can be given off, impedimenta to this will call forth distinct reactions. Thus it need not astonish us that impedimenta to the inspiration of oxygen will likewise immediately bring about phenomena.

That a decrease of oxygen pressure in inspired air does not immediately cause visible reactions to the respiration, might be explained as follows. Let us suppose that the barometric pressure is 760 mm; the pressure of the gases together in the alveolus will then amount also to 760 mm. These pressures are divided as follows:

1. The constant pressure of saturated water-vapour at body-temperature: this is 47 mm.

2. The pressure of nitrogen $\frac{80}{100} \times (760 - 47)$ is approx. 570 mm.

3. For carbondioxide a mean pressure of 40 mm is given.

Together 657 mm. Thus for oxygen 760—657 viz. about 100 mm, is left.

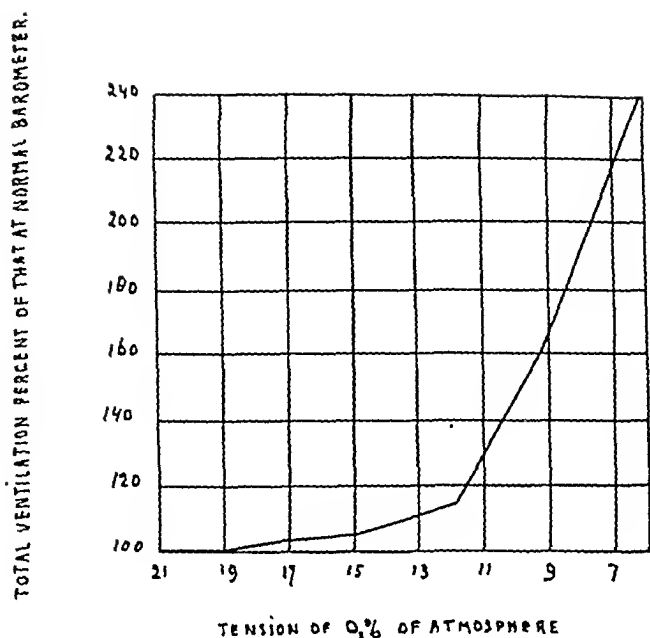
Jongbloed explains this as follows (28). Of the nitrogen in the atmospheric air nothing is taken up in the body. The percentage of nitrogen in the alveolar air remains the same as that in the atmospheric air, *i. e.* about 80 %. For oxygen and carbondioxide approx. 20 % is left. It will be a contest between the molecules of these two gases to gain the overhand, and here carbondioxide has an advantage, because it can enter the alveolus directly out of the blood, whereas the oxygen molecules have to take the longer way by the bronchi and bronchioli.

As the percentage of the other gases is about constant, only a percentage of about 15 % is left for the oxygen, corresponding

to a pressure of 100 mm although the pressure in atmospheric air is about 50 % higher.

Let us suppose that the oxygen percentage of atmospheric air falls to 19, that is, a decrease of 2 %, the nitrogen percentage will rise 2 %, which will cause a relatively very slight rise in the partial pressure. The difference of pressure between atmospheric air and alveolar air is thus very slight, whereas the difference of pressure between atmospheric oxygen and alveolar oxygen is still considerable. The slight rise in the partial pressure of nitrogen in the lung alveolus, however, will be still less, for a little more nitrogen will enter the blood plasma in physical solution and so much nitrogen will be withdrawn from the lung alveolus that the blood and the tissues of the organism will become saturated with it, corresponding to the somewhat higher pressure. Only then will this pressure continue to be higher. Before this, however, the nitrogen pressure will remain almost the same, namely 570 mm. This leaves for the oxygen again 100 mm. A diminution of the oxygen in atmospheric air of 2 %, therefore, need not per se be accompanied by a diminution in the pressure in the lung alveolus. In other words: the inhibition exercised by oxygen remains equal and no changes in respiration are likely to occur. If the diminution in the atmospheric air is so great that a pressure of 100 mm in the lung alveolus cannot be maintained, a hyperpnea will result.

In Best and Taylor (4) we found a diagram of Means (fig. 4) representing the increase of lung ventilation in relation to the decrease of oxygen pressure in atmospheric air. These experimental data agree particularly well with our theoretical considerations. It appears that, if the oxygen percentage in atmospheric air falls to 19, the respiration volume remains the same. Also the further course of the curve agrees completely with our theory. For with a further decrease in oxygen percentage the pressure of 100 mm in the lung alveolus will not be maintained. A hyperpnea will result. On account of this the air-renewal in the lung becomes better, and the alveolar carbondioxide pressure lower; in other words, the fall in alveolar oxygen pressure will not be proportionate to the fall in the atmospheric air. Only when hyperventilation no longer gives compensation *i. e.* when the oxygen pressure in the atmospheric air falls below 14.5 %, will a much stronger hyperpnea appear. Consequently the line becomes a curve as in the diagram.



EFFECT OF OXYGEN LACK UPON PULMONARY VENTILATION
IN HUMAN SUBJECT (AFTER MEANS)

Fig. 4.

A slight rise in carbondioxide pressure over 40 mm, causes an immediate hyperpnea, a slight fall in the oxygen pressure below 100 mm likewise.

Under normal conditions the organism need not take account of the surplus of oxygen available; therefore it stands to reason that there have been so many researches respecting the deficiency of oxygen in the blood. Only relatively few data are known of the influence which a lengthy stay in air with a high percentage of oxygen has on respiration. In these experiments oxygen was administered only to eliminate the influence of oxygen deficiency.

The phenomena that occur in the experiments of Euler and Liljestrand (12) were as follows: If in anaesthetized animals the respiration was switched over from atmospheric air to oxygen a great decrease of lung ventilation was observed. (The inhibition was increased.) After some time the effect diminished. (When the

ventilation is inhibited the carbondioxide pressure rises, till a balance is reached on a higher level.) When respiration was switched back to air again, an increase of ventilation was obtained greater than when first inhaling the air. (In switching over to air, the inhibition becomes of the same degree as during the first inspiration. There is still too high a carbondioxide pressure in the blood, however, so that the stimulus predominates.) After some minutes a balance is again attained. (The excess of carbondioxide is washed out by hyperventilation, till the original level is reached again.)

Hilding Bjurstedt (25) pointed out the fact that with strong hyperventilation on account of oxygen deficiency so much carbondioxide can be washed out, that a serious alkalosis is caused. In this alkalosis the central regulation by carbondioxide is entirely wanting, so that respiration is actuated only by the stimulus of oxygen deficiency via the chemo-receptors. (During a strong desaturation the inhibitory action of the oxygen is indeed much less, but respiration continues on account of the carbondioxide still present, even though the quantity is greatly diminished. The stimulus is on a very low level.) Oxygen administered in this condition may be highly dangerous, because then the last stimulus, namely oxygen deficiency, is gone. (Administration of oxygen in this condition increases inhibition so strongly, with respect to the low carbondioxide stimulus, that cessation of breathing may be the consequence.) If the alkalosis is less, the activity of the chemo-receptors becomes less and the respiratory centre takes part again in the regulation. (This explanation, whereby it is hypothetically accepted that the respiratory centre is eliminated, can be relinquished.)

The above-mentioned explanation need no longer be given for the sometimes very great rise in carbondioxide percentage as found in arterial blood of patients who had inspired oxygen a long time.

Assuming that oxygen has an inhibitory effect, desaturation in these patients will not only cease but the high oxygen pressure in the plasma will act as a strong inhibition on the lung ventilation. Owing to this, less carbondioxide will be washed out with the consequence that the percentage of carbondioxide in the lungs will rise. If we now look at the schema on page 237 and at the dissociation curve of bicarbonate on page 236, we can deduce that also a high alkaline reserve will be finally found.

Here follow some data obtained from patients with and without anoxemia. They were treated in an oxygen-tent for a considerable time (at least three days). The arterial blood was obtained by puncture of the femoral artery. The blood was collected and kept according to a method of my own (39). The gas analyses of the arterial blood were performed with Van Slyke's large apparatus; the determination of the alkaline reserve with the small apparatus of Van Slyke. The gas analyses of the alveolar air were performed with the Haldane's apparatus. In each first column the data are given obtained when atmospheric air was breathed, in each second column those when air was breathed of which the oxygen percentage was approx. 55.

If our hypothesis is correct, the high oxygen pressure will cause a strong inhibition, whereby the lung ventilation must decrease. The carbondioxide percentage in the alveolar air will then rise so much that after some time the greater stimulus from that gas will again be in equilibration with the stronger inhibition of oxygen. When we consider that an increase of the alveolar carbondioxide percentage by 0.17 % is already a doubling of the lung ventilation, an increase of even 3.39 %, with breathing perfectly normal, is not to be explained in any other way than by a strong inhibition on the high oxygen pressure. These phenomena also, when oxygen pressure increases, confirm our hypothesis. In the table we can also see the rise of the carbondioxide content of arterial blood, the alkaline reserve and the decrease of oxygen capacity. It is noticeable that in no. 1 and no. 3 an almost normal desaturation continued while the alveolar carbondioxide percentage rose by 2.34 and 3.39.

Though when publishing these data, I expressed the supposition that oxygen pressure in blood plasma has an inhibitory effect via the chemo-receptors, the investigation at that time was solely intended to bring to light the immense value of oxygen therapy in cases of anoxemia. The composition of alveolar air was investigated in order to find how high the oxygen percentage in it would become. Of a number of 27 patients only some were examined who were suitable for this investigation. In these analyses it further appeared that the carbondioxide percentage in the alveolar air rose considerably. In patient no. 3 the alveolar carbondioxide percentage fluctuated for 3 weeks round about 8.5 %. Not until the oxygen pressure became normal, did the alveolar carbondioxidepercentage fall again.

Vol. % O ₂ in art. blood		O ₂ -capacity Vol. %		Desatura- tion %		Vol. % CO ₂ in art. blood		Alkaline- reserve Vol. %		% O ₂ in alv. air		% CO ₂ in alv. air		Increas- alv. CO	
16.63	17.41	18.79	18.06	11.15	3.9	53.03	57.19			12		7.09	9.43	+ 2.34	
15.07	16.84	16.81	16.57	10.40	- 1.5	55.43	68.84								
15.86	17.12	18.26	17.91	13.20	4.4	45.83	59.77	52	72	12.67	48.42	5.46	8.83	+ 3.39	
18.87	21.47	21.27	21.25	11.20	- 1.0	45.79	55.79			11.46	55.73	6.37	9.32	+ 2.95	
19.66	19.07	20.43	19.23	3.50	0.8		52.48	58	62	11.22	58.28	6.22	7.55	+ 1.33	

It would be interesting to have normal testpersons for some days in an atmosphere with an oxygen percentage of *c. g.* 40; and then for some days with 50 % and 60 %. During that time the composition of the alveolar air should be examined daily, and the quantity of oxygen and carbondioxide in the arterial blood, and the alkaline reserve, be determined. This investigation, however, belongs rather to the field of the physiologist.

In order to investigate the influence of carbondioxide on the chemo-receptors the patients may not in my opinion, inspire this gas in oxygen. The results become confused owing to the influence of the high oxygen pressure.

The results we have obtained from the experiments upon the influence of the chemo-receptors of aorta and sinns carotiens on respiration have been summarized in five points at the beginning of Chapter V. Considering them again it appears that they can all be explained by assuming that oxygen has an inhibitory effect, while the results of the experiments as such can be unreservedly accepted. During life there will be continuously stimulation by carbondioxide and inhibition by oxygen, while the chemo-receptors provide for a quick and precise regulation. Since by hyperventilation the alveolar oxygen percentage can be raised till this is about equal to that of atmospheric air, it will be possible to raise the oxygen pressure in blood plasma about 50 % over the 100 mm, so that there is a considerable regulation margin for inhibition upwards, which is still further increased by decrease in the stimulus, since by hyperventilation carbondioxide is being washed out.

It is undeniable that the mechanism of reflex regulation of respiration has no equivalent in any instruments made by man.

respiration. The oxygen pressure in the lung alveolus determines the limit above which the carbondioxide pressure can stimulate respiration.

When the carbondioxide pressure is lowered the inhibition by the oxygen will be relatively predominant and an apnea may occur. Oxygen pressure, like carbondioxide pressure, has a constant influence on the breathing. These two pressures are balanced, so that we can speak of a regulation level which, under special conditions, may be higher or lower than normal.

Changes in the partial pressure of one of these gases above or below the level will be followed by a change in lung ventilation. This subtle regulation of the chemical influences takes place via the chemo-receptors.

The relation between oxygen- and carbondioxide pressure is shown in a diagram.

Our experiments indicated that by raising the alveolar oxygen pressure, the alveolar carbondioxide percentage could rise to over 9 %, while the breathing remained absolutely quiet. This was accompanied by a rise in the arterial carbondioxide percentage and in the alkaline reserve.

Because our organism is placed in an atmosphere with a fixed oxygen percentage of 20.94, the alveolar oxygen pressure will, under normal conditions, be 100 mm, and consequently the alveolar carbondioxide pressure will be 40 mm.

An explanation is given for the absence of hyperventilation even when the atmospheric oxygen percentage is reduced to 19 %.

With this theory all the changes in respiration, found up till now, and caused by changes in oxygen- or carbondioxide pressure, can be made perfectly intelligible.

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Kidney Complications during Sulphonamide Therapy.¹

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The most serious drawback in sulphonamide treatment is the tendency of the sulphonamides to produce renal complications. In view of the extensive use of sulphonamides, kidney troubles rarely appear in this Country, if one can judge by the number of cases hitherto published. Here, in Denmark, eight cases in all have been reported of sulphonamide anuria (Lebel, Schroeder and Sinesen, 1940, Nissen and Roelsgaard 1940, Schroeder 1941, Bechgaard and Vermehren, 1941, Fogh, 1941 (2 cases), Kaae 1944 (2 cases)).

The sulphonamide administered was sulphapyridine in 5 cases, sulphathiazole in 2 cases, and in one case »Lucosil» (Sulfamethylthiodiazole). All the patients recovered after ureteral catheterisation and irrigation with a solution of sodium bicarbonate, but in one case (Schroeder 1941) bi-lateral ureterostomy was necessary.

At Bispebjerg Hospital during the past 1½ years, we have, however, come across a series of cases which indicate that sulphonamide anuria is neither rare, nor without risk. Several cases have proved fatal, in spite of intensive treatment.

Before giving an account of our observations, a few words will be said concerning the type and frequency of kidney injuries.

¹ Given in abbreviated form at the Danish Society of Internal Medicine 29/11/46.

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Frequency.

It is difficult to give the exact figures for the frequency of kidney complications, as these vary according to the sulphonamide employed, the duration of the treatment and the precautions taken during the treatment.

In the first years of sulphonamide therapy, when the sparingly soluble sulphapyridine was the compound usually administered, kidney troubles were without doubt considerably more frequent than they are now.

Plummer and Ensworth (1939) discovered seven cases of kidney damage amongst 270 patients treated with sulphapyridine, and, of these, two developed macroscopic hematuria and two anuria, one case of which proved fatal.

Brown, Thornton and Wilson (1940) had in 100 patients, 4 cases of anuria, one of which was fatal.

In this Country, Nissen and Roelsgaard (1939) found that of 41 patients, 10 were suffering from microscopic hematuria and five from macroscopic hematuria. One patient developed anuria and there were no deaths.

Flippin, Schwartz and Rose (1940) found microscopic hematuria in 6 cases from 100 patients under sulphathiazole treatment — there were no cases of anuria.

Jacobsson (1944) investigated the side-effects in 440 sulphathiazole-treated patients at Sabbatsberg Hospital (Stockholm). Two of these died, one on account of crystalline deposits and one from toxic reactions in the kidney.

The largest work has been published by Vilter and Blankenhorn (1944) who have reported cases of side-effects during 4 years of sulphonamide therapy at the Cincinnati General Hospital. In this period, altogether 1,936 patients were treated with sulphonamides, chiefly sulphathiazole, sulphadiazine and sulphapyrazine. Forty of these (approx. 2 %) developed kidney trouble. Eleven of these cases proved fatal, and 6 (approx. $\frac{1}{4}$ %) were entirely due to the kidney complications.

Type of Renal Injury.

The types of kidney damage can be roughly classified as follows (after Murphy and collaborators 1944):

- (1) Mechanical extrarenal.
- (2) Mechanical intrarenal.
- (3) Toxic intrarenal.

The first of these types of injury is by far the most common. The previously mentioned 8 cases of anuria that have been published in this Country all belong to this group. The characteristics of the condition have been thoroughly described by the authors quoted, and will only be repeated here in brief. Owing to the sparingly soluble nature of sulphapyridine and sulphathiazole, crystalline deposits of these drugs, or of their still less soluble acetylation products, are formed in the pelvis and ureters, and frequently in the bladder as well. A mechanical blockage of the urinary tract is thereby caused.

The symptoms are pains in the loin, hematuria, crystals in the urine, oliguria and eventually anuria if the condition is bilateral.

The diagnosis gives no difficulty as a rule and the prognosis is good, provided the appropriate treatment is promptly instituted, *i. e.* cystoscopy with ureteral catheterisation and removal of the crystals by means of catheter irrigation with a bicarbonate solution.

As mentioned before, all the reported cases recovered, but it has come to our knowledge that there have been fatal cases of mechanical anuria in this Country which have not been published.

In the intrarenal mechanical type, the mechanism is identical with that of the extrarenal, but the crystalline deposits are formed in the uriniferous tubules themselves, usually in the collecting tubules, but sometimes also in the convoluted tubules.

This form is rare, but the prognosis extremely serious. The symptoms are similar to those in extrarenal mechanical complications but on cystoscopy, no crystals in the bladder are found and the ureter catheter can, without resistance, be passed into the pelvis. Irrigation of the pelvis with a solution of sodium bicarbonate is usually without effect, and if diuresis does not ensue on intravenous fluid injection the patient will succumb.

In section, the kidneys are oedematous, swollen and with greyish striae in the pyramids which radiate fan-like towards the cortex.

Microscopical examination show the collecting tubules filled with an amorphous mass which often contains numerous round cells. The crystals cannot be seen by the customary method of preparation as they are dissolved by the reagents. Occasionally one finds a combination of the mechanical intrarenal and the mechanical extrarenal types. In this case diuresis cannot be effected by ureter catheterisation.

The last form of injury is the toxic intrarenal, and it is the

rarest and apparently the most serious. This type, which has only become more familiar during the latter years must be discussed more fully. No crystalline deposits are formed in the uriferous tubules, but the sulphonamides cause a toxic degeneration of the convoluted tubules, somewhat similar to the injuries due to mercuric chloride or carbon tetrachloride poisoning.

The symptoms of the toxic reaction are often less acute than in the other two types. Pains in the loin may be absent (Vilter and Blankenhorn, 1944); albuminuria, hematuria, cylindruria and oliguria are usually the signs which can lead to anuria. At times, the pathological content of the urine is amazingly small. It seems, therefore, evident that there is difficulty in making a differential diagnosis *in vivo*, between this type of reaction and the previous ones. In some cases a combination of *both forms* is seen.

The microscopical picture is very characteristic; the glomeruli are usually only slightly changed, but the cells of the tubules are, however, disintegrated with ill-defined cell boundaries, the nuclei are poorly stained and there is degeneration of the epithelium. The lumen of the convoluted tubules are frequently distended with corneous, hyaline and epithelial cell casts. Furthermore, an extensive focal round-cell infiltration may be seen, and sometimes thrombosis in the interlobular veins. A more detailed account is given by Bergstrand (1944).

As a rule the picture is easily distinguishable from the damage possibly caused by the primary condition (the infection). These changes can, moreover, also be seen in cases where sulphonamides are administered for common infections of the urinary tract, which could not be the cause of degeneration of the kidney. Finally, identical histological changes can be produced by the administration of sulphonamides to healthy experimental animals (Antopol and Robinson, 1940).

The first clinical cases seem to have been observed by Smith (1939). These were succeeded by a series of reports made by Pepper and Horaek (1940), Hellwig and Reed (1942), Lederer and Rosenblatt (1942), Hoyne and Larimore (1941), Winson and Burch (1942), Luetscher and Blackman (1943), Murphy and Wood (1943). Maisel, Kubik and Ayer (1944).

From Norway and Sweden cases have been reported by Wird (1942), von Porat (1944), Boysen (1945), Hagtvet (1946) and others.

In several of these cases the toxic reactions in the kidney have

been accompanied by focal necrosis with round-cell infiltration in the liver, lungs, spleen, lymph glands and suprarenals, also by round-cell infiltration into the myocardium.

The changes are supposed to depend either on a direct chemical action on the cells of the tubules or on hypersensitivity towards the sulphonamides.

In 1946 Bergstrand gave a description of 12 cases of this kind, and compared the histological picture with that appearing in «the crush syndrome».

Independently of Bergstrand, Trneta and collaborators (1946) drew attention to the fact that by experimentally evoking «the crush syndrome» by clamping off the hind leg of an animal, the kidneys exhibit a histological picture similar to the changes in «sulpha kidney», «incompatible transfusion kidney», Weil's disease and certain forms of nephritis. They have, moreover, shown that on carrying out this experiment, a cortical ischaemia in the kidneys is produced as the bloodstream, owing to subcortical vessel anastomosis is «short circuited», thus preventing the blood flow from reaching the cortex. In prolonged ischaemia damage to the cells of the tubules arises, and anuria. The mechanism in question is considered originally to have acted as a measure of defence on the part of the organism, in order to prevent the toxic substances from reaching the cortex of the kidney. It must be emphasised that Husfeldt and Bjerring already in 1935 entertained a similar theory of kidney injuries subsequent to traumatic shock.

In our own material we have seen examples of all three conditions of injury.

Case Reports.

The table shows, that there have been, all told, 11 cases of sulphonamide kidney complications. In two of these cases the same patient was concerned with a six months interval (Nos. 9a and 9b).

Seven of the cases are mechanical extrarenal, one is mechanical intrarenal, two are toxic intrarenal and one is believed to be toxic intrarenal.

The table also shows that the majority of cases seven in all, were in women.

The ages vary between 23 and 87 years with an average of 45.

Attention should be drawn to the fact that kidney damage can also occur in children. Murphy and his collaborators had a patient who was only 1 year old.

Table

No.	Sex	Age	Treated for	Treated by	Sulphonamide employed	Total dosage
1	Female	56	Pneumonia	Own Doctor	Sulphapyridine	5.0 g
2	Female	30	Gonorrhoea	Veneral Dept.	Sulphathiazole	27.0 g
3	Female	55	Pneumonia	Medical Dept.	Sulphathiazole	20.0 g
4	Male	54	Pneumonia	Own Doctor	Sulphathiazole	11.0 g
5	Female	87	Pneumonia	Medical Dept.	Sulphathiazole	15.0 g
6	Female	23	Gonorrhoea	Own Doctor	Sulphathiazole	10.0 g
7	Female	34	Gonorrhoea	Gynaecological Poliklinic	Sulphathiazole	27.0 g
8	Female	35	Gonorrhoea	Veneral Dept.	Sulphathiazole	10.0 g
9a	Male	24	Pneumonia	Medical Dept.	Sulphanilamide Sulphathiazole »Lucosil»	2.4 g 4.0 g 13.0 g
9b			Pneumonia	Medical Dept.	Sulphathiazole »Lucosil»	20.0 g 4.0 g
10	Male	27	App. Acute Peritonitis	Surgical Dept.	Sulphathiazole »Lucosil» locally »Lucosil» intramusc.	20.0 g App. 4.0 g 20.0 g App.

Sulphathiazole is the substance which, in our cases has most frequently given rise to kidney troubles, primarily because it is the sulphonamide which is chiefly employed in this country.

Sulphapyridine, which is even more sparingly soluble than sulphathiazole, only participates in one case, solely due to the substance being out of use.

»Lucosil», which is especially used because of its relatively high degree of solubility, though it has the disadvantage of being

1.

Renal symptoms developed after days	Type of renal injury	Treatment	Progress	Autopsy
1 5 3 2 3 ? 2	Mechanical Extrarenal d:o	Bicarbonate Intravenously d:o	Recovered d:o d:o d:o d:o d:o d:o	
3	Mechanical Intrarenal	Bicarbonate Intravenously Ureter Catheterisation Sympathetic Blockage Diathermy	Died	Anuria. Degen. Renal Parenchyma Degen. Hepatic d:o. Degen. Myocardiac d:o. Pericarditis fibrin. Pleuritis d:o
3	Toxic Intrarenal	Bicarbonate Intravenously	Recovered	
3	d:o	d:o ureter cath. decapsulation kidney	Died	Interstitial nephr. fibrinous pericard. d:o pleur. Pulmonary oedema
3	Supposed Toxic	Bicarb. intrav. Na-Sulphate Intrav. Ureter Catheterisation	Died	Acute Appendicitis sequ. Diffuse peritonitis Hemorrhagia in Ureter, Pelvis & Urinary bladder Organ deg. Parenchyma

excreted slightly too quickly, has, when combined with sulphathiazole, been the cause of three fatal cases of toxic intrarenal damage to the kidneys. It is highly significant that renal injuries have not arisen subsequent to strikingly large doses. The average dose is only 21 g and in one case the dose was no more than 5 g sulphapyridine. This corresponds with the results of several other investigators. »The quantity of the drug used, bears little or no relation to renal injury» (Murphy and collaborators 1944). The

average dose in Murphy's material was 20 g, and in a single case was as small as 0.6 g.

It should be mentioned, however, that in four of our cases, anuria developed in gonorrhoea patients subsequent to a brief therapeutic course using large doses (9—10 g for 2—3 days). After such doses, the concentration of sulphonamide in the organism can easily become so high that sulphonamide crystals are deposited in the urinary tract if special precautions are not taken.

As regards those diseases which have been treated with sulphonamides, it can be seen that apart from one case of peritonitis, we have been exclusively concerned with pneumonia and gonorrhoea. In one case of suspected pneumonia (9b), however, there were no definite changes detectable by the stethoscope, but on the whole it must be said that sulphonamide therapy has in all the cases been fully indicated.

It is furthermore seen, that in only three of the cases has sulphonamide treatment been carried out by the patient's own doctor. The remaining cases have arisen during treatment in a hospital ward or at a polyclinic. Only two of the cases have developed at Bispebjerg Hospital (Patients Nos. 5 and 10), the remainder having been transferred here or admitted direct from the home.

Lastly, it is seen that the latent periods dating from the commencement of sulphonamide treatment to the appearance of symptoms of kidney damage, varies from one to five days, with an average of three days.

In one case, anuria manifested itself subsequent to the patient's discharge from a hospital ward (Patient No. 2).

The patient was a woman of 30 years who was admitted to Bispebjerg Hospital 24/11/45, suffering from anuria subsequent to sulphathiazole treatment. Two months previously gonorrhoea was diagnosed at a polyclinic. She received, as an out-patient, a three-day course of sulphathiazole treatment, but this having no effect she was admitted (19/11/45) as an in-patient for combined sulphathiazole and fever treatment. The first three days she was given 8 g sulphathiazole daily, in all 27 g + fever treatment, after which she was discharged on the fourth day. At the time of discharge she felt unwell with considerable pains in the abdomen and lumbar region, but made no mention of this to the staff. Having reached her home she felt dizzy with nausea and several attacks of vomiting, and the following day she called the doctor who referred her to hospital with the above-mentioned diagnosis.

On admittance, the patient was pale and sallow, there were numerous watery vomitings, temperature 37.3°, pulse 72, and tenderness in the right loin.

After a subcutaneous injection of 1 ml doryl, the patient passed 100 ml urine in which some reddish brown crystals were found.

Microscopic Examination of the Urine:

+	Leucocytes
+++	Erythrocytes
0	Casts
++	Crystals
+	Albumin.

Blood Urea 170 mg/100 ml. B.P. 115/65.

Sodium bicarbonate was immediately administered.....

1.3 %	1 litre subcutaneously
6 %	1 litre subcutaneously
1.3 %	1½ litre intravenously

And later Glucose Solution
Also Sodium Bicarbonate Solution
after which diuresis set in, and blood urea fell to 64 mg/100 ml in the course of 5 days.

The patient was discharged in good condition 2/12/45.

This case history is given because it is a typical example of sulphonamide anuria during the treatment of gonorrhoea with heavy doses of sulphathiazole, and because it indicates the advisability of observing the patient after cessation of the treatment.

The other cases of anuria of mechanical extrarenal origin, show nothing new and will not be further discussed. The case of mechanical intrarenal and those of toxic intrarenal anuria, will however, be given in detail.

Mechanical Intrarenal Anuria.

A female patient of 35 years who (29/11/45) was admitted to Ward 'D' suffering from anuria subsequent to sulphathiazole dosage. She had previously been well until, approximately 6 weeks before admittance, gonorrhoea was diagnosed, and she was treated as an out-patient, with 25 g sulphathiazole in the course of three days. During the treatment there was intense nausea with pyrexia.

As this treatment had no effect she was admitted to the venereal department (24/11/45), and the same day received altogether 10 g sulphathiazole and fever vaccine. The following day there was nausea and headache, she was breathless and cyanotic and the treatment was therefore stopped. The day after, universal rash and conjunctivitis set in, and the temperature rose to 39.2° C. 27/11 urinary output was only 200 ml, and 900 ml, 1.3 % sodium bicarbonate solution was injected intravenously, but was without effect on the diuresis. After 12 hours of complete anuria, the patient was transferred to Bispebjerg Hospital (27/11/45).

On examination the patient was exhausted, atonic, congested with slight lip cyanosis. — Temperature 38.9° C. Pulse 108. — The tongue was coated.

Pulmonary & Cardiac Auscultation: Normal.

Abdomen: Soft, undistended, slight tenderness in the left lumbar region.

On the extensor surface of the extremities a vesico-papular eruption was seen. There was bilateral conjunctivitis.

On catheterisation, approximately 50 ml urine was evacuated, which was not macroscopically hemorrhagic, but contained a number of crystals.

Microscopic Findings in Urine:

- + Leucocytes
- (+) Erythrocytes
- 0 Casts
- + Crystals
- + Albumin
- 0 Bacteria.

Blood urea: 190 mg/100 ml.

One litre glucose saline solution was given subcutaneously, but as anuria persisted cystoscopy was performed, 28/11. This showed the presence of a few ml slightly turbid urine. The mucous membrane was normal and there was no sign of concretions. Both ureters were easily catheterised and the catheters were inserted 20 cm and allowed to remain. The ducts were then irrigated with sodium bicarbonate solution.

The next day approx. 100 ml urine containing blood was passed, followed by total anuria in spite of treatment with bicarbonate and glucose solutions, »sympathetic nerve blockage» and diathermy of the lumbar regions. The patient became increasingly uraemic (blood urea 1/12, 333 mg/100 ml) and *sub finem*, the temperature rose to 42.2° on 5/12, there was abundant spontaneous micturition in the bed, but the patient died in hyperpyrexia 17 hours later.

Summary of Autopsy Report. (Pathologist Bj. Vimtrup.)

Lungs are large and firm. In section considerable oedema and stasis can be seen. There is no certain indication of pneumonia.

Heart: No sign of pericarditis or endocarditis. The myocardium seems rather grey in section with an ill-defined outline showing parenchymatous degeneration.

Liver: The outline on surface section ill-defined, parenchymatous degeneration.

Kidneys: Both are large and flabby, somewhat dark in colour and with the vessel outlines intensified. On loosening the capsule slightly, the surface is completely smooth and the consistency very soft. In section, the natural outlines are rather ill-defined, excepting that, the cortical tissue between the pyramids stands out conspicuously. The striae in the cortex are still present and pelvis, ureters and bladder show nothing abnormal.

Microscopic Examination of the Kidney Tissue (Fig. 1 & 2).

Using Mallory dye on Zenker-fixed material, pronounced degenerative changes are seen in the kidney, and there is considerable distension of

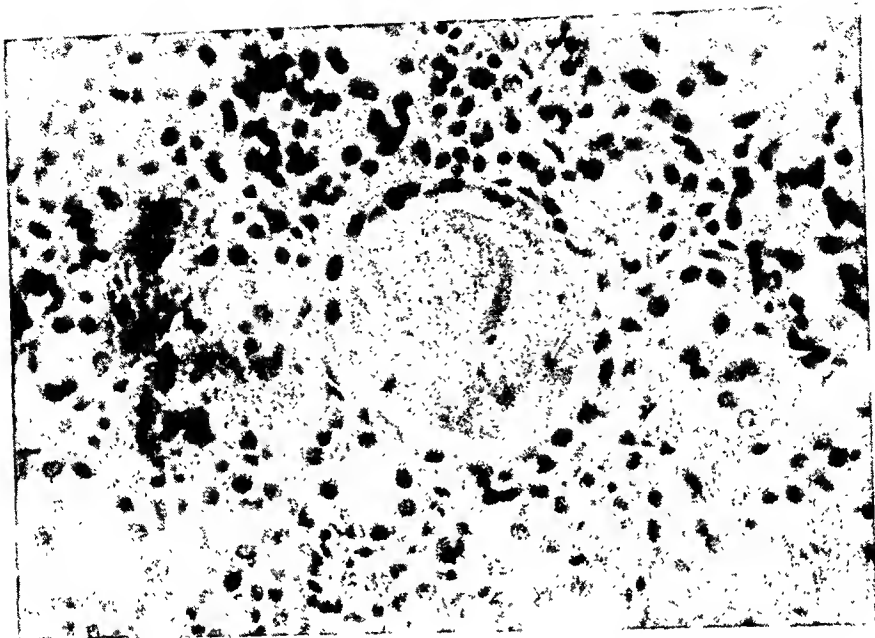


Fig. 1. Section of the kidney. A collecting tubule in the centre, filled with an amorphous mass.

the blood vessels. Furthermore, one finds in this preparation, in the straight tubules, though not in all of them, but in both medullary rays and pyramids, the scattered appearance of conglomerations of an amorphous mass, which is stained a deep violet blue colour. In some ducts are found moreover, apart from those amorphous masses distributed in small clusters, a multitude of cells, some of which are leucocytes and others dislodged epithelial cells. These cells are also intensely stained and incidentally much darker than the cell nuclei, which surely must indicate the presence of calcium.

These conglomerations in the tubules are dispersed, often in a somewhat striated manner. Large, dislodged epithelial cells can also be seen lying in the collecting tubules, but the epithelia of these are usually intact.

In a Gieson preparation of the kidney, a very conspicuous hyperemia is found in the cortex. The glomeruli are large, the capsular space slightly enlarged and notably the capillaries in the most superficial part of the cortex are dilated and filled with blood. Some interstitial infiltration with mono-nuclear cells is seen, together with conglomerations of leucocytes and detached epithelial cells in the various tubules, but chiefly in the convoluted tubules.

In the pyramids, hyperemia is likewise discovered, with numerous polymorphonuclear leucocytes in the blood vessels and plasma cells, as well as leucocytes and lymphocytes interstitially. Occasionally, hyaline casts are seen and the tissue seems slightly oedematous. Towards the apex of the pyramids, numerous collecting tubules, frequently

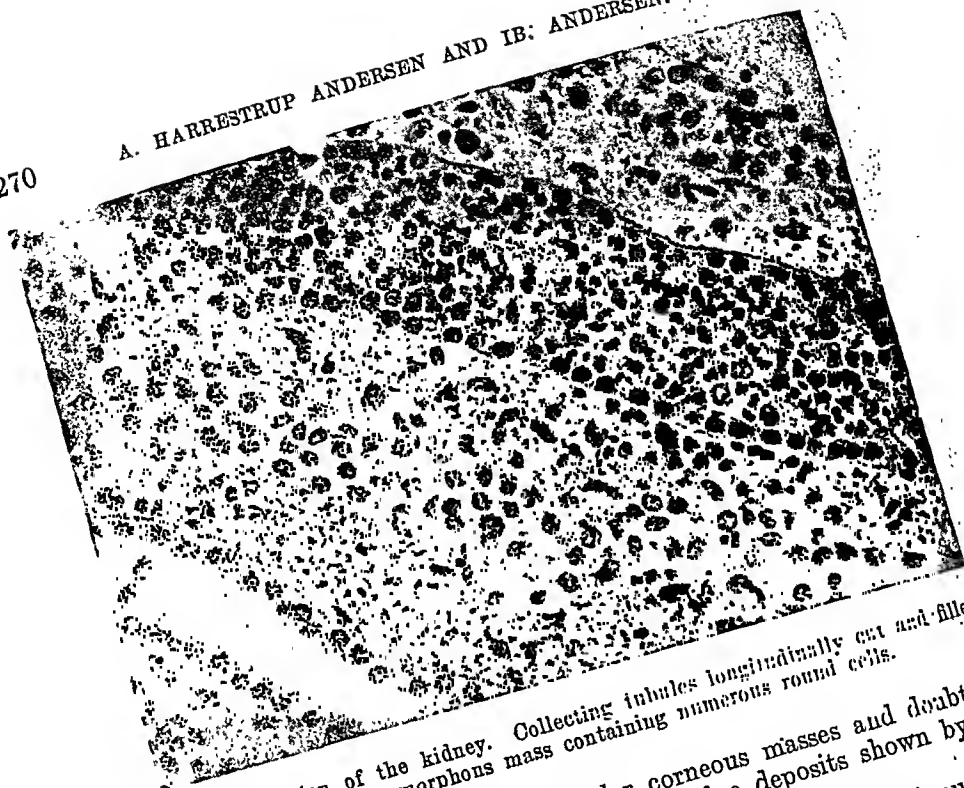


Fig. 2. Section of the kidney. Collecting tubules longitudinally cut and filled with and amorphous mass containing numerous round cells.

in groups, are packed with irregular corneous masses and doubtless correspond to the intensely conspicuous blue deposits shown by the previous staining method.

In a section of the liver, central stasis is found in the acini, augmentation of the Kupffer cells, and some peripheral fat infiltration. A section of the myocardium shows the transverse striation more or less preserved, and the nuclei appear normal. There is no swelling of the muscle fibres, but some scattered infiltration with leucocytes and mono-nuclear cells, together with oedema and hyperaemia.

The histological investigation has thus revealed central stasis of the liver acini with commencing degeneration; peripheral fat infiltration in the liver; increased lipofuscin in the musculature of the heart, and commencing myocarditis. In the kidney, deposits of amorphous masses are found, which are stained blue-purple by hematoxylin. These masses appear packed in the collecting tubules and can also be seen together with leucocytes and dislodged epithelial cells, in the convoluted tubules. There is, moreover, very marked hyperemia in the peripheral cortical zone, and some interstitial reaction.

To summarize: A woman 35 years old, subsequent to treatment with 10 g sulphathiazole and fever vaccine for chemo-resistant gonorrhoea, gets nausea, vomiting and medicamental exanthema. Three days later, total anuria develops which leads to her death in the course of 8 days. On cystoscopy, there is no indication of concretions in the urinary passages.

Autopsy shows that the anuria is mechanical intrarenal caused by

KIDNEY COMPLICATIONS.

deposits in the uriniferous tubules, primarily in the collecting tubules. Degeneration of the liver, and commencing myocarditis are also found.

Toxic Intrarenal Anuria.

Man of 24, previously fit; 5/7/45 he was admitted to hospital after being treated at home for five days in vain, for a febrile infection with a rise of temperature to approx. 40° C. At home he received in all 2.4 g sulphanimide. After admittance, sulphathiazole was prescribed as the patient was thought to be suffering from pneumonia, but after administration of 4 g, the sulphathiazole was stopped on account of nausea and vomiting, and then altogether 13 g of «Lucosil» was given. Under this treatment, the temperature fell to 37.2° C, but simultaneously, the diuresis began to decrease (5/7 2,200 ml, 6/7 640 ml, 7/7 300 ml, 8/7 90 ml, 9/7 90 ml, 10/7 80 ml, 11/7 0 ml, 12/7 100 ml) inspite of liberal treatment with saline solution and bicarbonate. 12/7 the patient was transferred to Bispebjerg Hospital for anuria.

Blood Urea 10/7 was 127 mg/100 ml.

Microscopic Examination of Urine 11/7 showed a few leucocytes, otherwise nothing.

In micro-lumbar anaesthesia, cystoscopy was performed and revealed an empty bladder with no crystals. Both ureter ostia were normal and were easily catheterised in full length without encountering the slightest obstruction. Both pelvis were irrigated with isotonic bicarbonate solution, and the return flow was clear. As no indication was found of mechanical obstruction of urine secretion, the patient was moved back again.

Shortly after the transfer, the patient micturated spontaneously. Diuresis 12/7 was 650 ml and increased steadily to 5,200 ml 17/7, and during the next few weeks was 2—3 litres. At the same time, the blood urea fell from 297 mg/100 ml 14/7 to normal. For the first week the urine contained albumin.

Microscopic examination of Urine showed some hyaline casts and leucocytes, but no erythrocytes.

Ophthalmoscopy 13/7, was normal with no sign of retinitis.

The patient was discharged 13/8, in good condition. After this, he felt perfectly fit until six months later — 22/1/46 — he was once more admitted to the same department with a febrile infection which had been treated for three days at home with sulphathiazole, 20 g in all, but without effect.

On admittance, the temperature was 40° C. and the patient complained of nausea, pains in the epigastrium, and repeated vomiting. On chest examination slight dullness could be heard on the right dorsal surface, with no crepitation.

«Lucosil» was administered but after a dosage of altogether 4 g the drug was stopped on account of nausea and vomiting. The subsequent days, diuresis decreased (23/1 275 ml, 24/1 25 ml, 25/1 200 ml, 26/1 0 ml and 27/1 0 ml).

Microscopical Findings in the Urine:

23/1/46	24/1/46	25/1/46
+ Albumin	+ Albumin	+ Albumin
0 Erythrocytes	0 Erythrocytes	+ Erythrocytes
0 Leucocytes	0 Leucocytes	+ Leucocytes
0 Casts	0 Casts	0 Casts
		++ Crystals

Blood Urea:

23/1/46	27/1/46	28/1/46
112 mg/100 ml	210 mg/100 ml	261 mg/100 ml.
100/70 B.P.	130/95 B.P.	

28/1 a few ml urine were passed.

Microscopical Examination of Urine:

- ++ Erythrocytes
- +++ Leucocytes
- + Corneous Casts
- (+) Crystals
- ++ Albumin

He was then transferred to Bispebjerg Hospital for cystoscopy.

Objective examination found the patient exhausted, but orientated, with violent hiccoughs, dry lips and moist tongue.

Pulmonary & Cardiac Auscultation: Normal.

Abdomen: Soft and distended: meteoristic.

Extremities: Slight oedema of both thighs.

Under lumbar anaesthesia, cystoscopy with ureter catheterisation was performed and the bladder found quite empty and containing no visible crystals or concretions. The mucous membrane of the bladder was normal and the ureter ostia contracted rhythmically, but without emitting urine. Both ureters were then catheterised in full length without difficulty, but no urine was evacuated. The ureters were then irrigated through the catheters with isotonic sodium bicarbonate solution, the return flow was clear, and the catheters were left in place.

Four hours after ureter catheterisation, not one drop of urine had been passed, and the decision was therefore made to decapsulate the left kidney; the tissues were slightly oedematous and the left kidney was immediately located, and was large with a perfectly smooth surface of normal colour. The fibrous capsule was very easily loosened and there was only slight bleeding. One dared not submit the patient also to a decapsulation of the right kidney and

Sodium sulphate was administered 200 ml intravenously and

Sodium bicarbonate solution 1.3 % 900 ml subcutaneously.

In spite of abundant use of:

Saline solution

Sodium bicarbonate solution

Euphyllin

Nicaetamide and

Sodium sulphate solution,

the patient weakened.

At 7.50 p.m. coffee-grain vomiting occurred, during which death ensued.

Summary of Autopsy Report. (By Bj. Vimtrup, senior pathologist.)

Pleura: Some fibrinous coating, otherwise normal.

Lungs: Large: of increased consistency and dark in colour. The cut surface oozes a frothy, serous fluid, but is also intensely congested.

There is no indication of pneumonia or infarction.

Pericardium: Coated with a fibrinous covering. Endocardium normal. Valves normal. The myocardium is pale, oedematous, but with no sign of myocarditis.

Liver: The tissue is slightly oedematous, but is otherwise normal.

Spleen: Cut surface exposes swelling of the follicular tissue and decay of the pulp tissue.

Kidney: The capsule is easily loosened and the surface smooth and shining with emphasised vessel definition. The cut surface shows enormous oedema of the interstitial tissue and increased vessel outlines.

Urinary Tract: Normal.

Autopsy Diagnosis:

Anuria.

Acute Nephritis.

Uraemic fibrous pericarditis.

Uraemic fibrous pleurisy.

Pulmonary oedema.

Microscopical Examination of the Kidney Tissue (Fig. 3):

The selected samples exhibit a pathologically changed renal tissue. The pathological processes seem primarily to have affected the connective tissue of the kidney, as it is here one finds an extremely intense hyperemia and excessive infiltration of inflammatory cells. This primarily involves lymphocytes and plasma cells, but in certain areas, a few polynuclear leucocytes are also present. This is a case of diffuse infiltration. There is no abscess formation, and no localisation of inflammatory cells along the medullary rays, so characteristic of ascending nephritis. The glomeruli seem to be remarkably little affected by the process. There is no leucocyte infiltration in the stroma and no fibrosis or hyalinisation. There is no sign of proliferation of the epithelial cells of the capsule, but albumin detected in the Bowman's capsular space and likewise hyaline casts in the first and second convoluted tubules. The kidney tubules give an exhausted impression. They are narrow, and the epithelial cells are dislodged and seem to be degenerating, but here as always, one must judge cautiously on account of the well-known rapidity of *post mortem* changes.

Histological Diagnosis:

Subacute interstitial nephritis.

To summarize. A man of 24 years developed, subsequent to dosages of 2.4 g sulphanilamide, 4 g sulphathiazole and 13 g «Incasil», a pronounced oliguria which nearly terminated in anuria. The microscopical picture of the urine, showed nothing abnormal apart from a few leucocytes. Anuria was relieved, possibly after lumbar anaesthesia and was

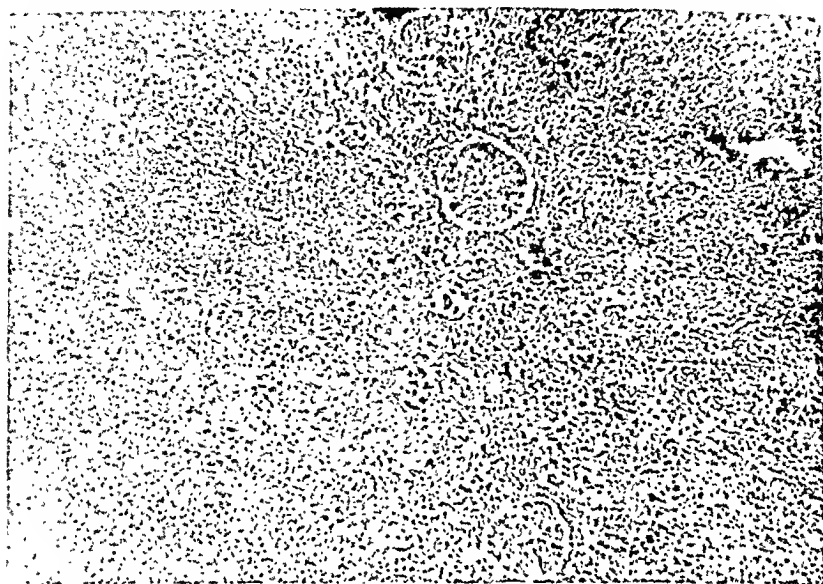


Fig. 3. Section from the kidney showing excessive interstitial round-cell infiltration and hyperemia. The glomeruli are intact.

succeeded by polyuria. During the first week, the urine contained albumin, casts and leucocytes, but no erythrocytes.

The patient was discharged in a fit state without any indication of permanent kidney trouble.

Six months later, he again developed oliguria after dosages of approx. 20 g sulphathiazole and 4 g »Lucosil». The urine contained albumin and later, leucocytes, erythrocytes and crystals. On performing cystoscopy no sign of mechanical anuria could be found, but in spite of intensive fluid administration and decapsulation of the left kidney, the patient died in uremia.

Autopsy showed interstitial round-cell infiltration of the kidneys and degeneration of the tubules. There was no indication of mechanical anuria.

The picture is typical, for a case of toxic sulphonamide anuria.

Supposed Toxic Intrarenal Anuria.

A man of 27 years was admitted 4/2/46 for acute appendicitis. He had been previously fit, apart from some kidney trouble ten years before, when he had passed two urteric calculi *per urethram*. There had been no kidney trouble since.

The patient was ill for 36 hours preceding admission, with pains in the entire abdomen radiating down towards the right iliac fossa.

Objective examination showed slight exhaustion, moist tongue.

Pulmonary and Cardiac Auscultation: Normal.

Abdomen: Generally tense and tender and quite hard. Temperature 38° C. Pulse 116.

Laparotomy and appendicectomy were instantly performed. There was a slightly turbid fluid in the peritoneal cavity. The appendix lay in a retro-cecal position and was large, swollen and red with a perforation at the base. It was removed retro-cecally and 10 g »Lucosil« was applied to the wound.

Administered:

»Insipidin« and Saline Solution 1 litre subcutaneously.

5/2. Pulse 104. Temperature 38.9° C.

Administered:

»Lucosil« 5 ml four-hourly.

Diuresis 5/2. 200 ml.

Urine Microscopy:

- + Leucocytes
- 0 Erythrocytes
- 0 Casts
- + Crystals
- + Bacteria
- 0 Albumin.

Diuresis 6/2. 650 ml

after which complete anuria set in until death ensued 3 days later.

»Lucosil« treatment suspended 8/2 after having administered approximately 25 g.

Blood Urea 9/2 290 mg/100 ml.

The patient weakened during the following days as a result of diffuse peritonitis, paralytic ileus and uremia.

9/2 a second laparotomy with enterostomy was performed and cystoscopy on 10/2. There were clots in the bladder and fresh bleeding. With constant irrigation the ureter ostia were finally found and catheters inserted bilaterally and allowed to remain.

11/2. Ureter catheterisation failed, at 8.15 a.m. death ensued.

Summary of Autopsy Report.

Lungs: Consistency widely increased. Cut surfaces very moist, oozing a serous fluid, no sign of pneumonia.

Heart: Normal.

Alimentary Canal: Small intestine slightly dilated and with a fine fibrinous coating. The seat of the appendix seems satisfactory.

Liver: Cut surface is normal.

Kidneys: The capsule is easily removed. On the left side some small cysts can be seen. The cut surface shows oedema of the parenchyma and also scattered cysts, ranging from the size of a pea, to that of a hazel-nut. No crystals are to be seen, but on the right side, there are some coagula in the pelvis and ureter.

Bladder contains large coagulum and ecchymotic areas but no sign of sulphonamide crystals.

Autopsy Diagnosis:

Acute appendicitis with sequelae, fibro-purulent diffuse peritonitis, stasis, kidney cysts, hemorrhages into ureters, kidney, pelvis and bladder; organic parenchymatous degeneration.

Microscopy of the Kidneys.

In paraffin sections which are stained in various ways, very considerable hyperemia is seen in many glomeruli and blood in the capsular space around the glomeruli. The epithelium of Bowman's capsule is slightly hyperplastic. In several convoluted tubules, degenerating red blood corpuscles may be found and erythrocytes are also seen in the small collecting tubules. The epithelium, however, is relatively intact and oddly enough the striated borders are apparent in the first convoluted tubule. The interstitial tissue in the kidney is not appreciably increased and there is no inflammatory infiltration.

In some collecting tubules granular masses are seen, which are stained yellow with picric acid but one can hardly judge whether they are degenerating red blood corpuscles or precipitates; the latter is the most likely. In the liver, there is swelling of the cells and chromatolysis.

Microscopic Diagnosis:

Degenerated parenchyma in the liver. Glomerulitis hemorrhagia.

To Summarize:

A twenty-seven year old man is operated for acute perforative appendicitis. 10 g «Lucosil» is applied intraperitoneally, and, in all, 25 g «Lucosil» is also given intramuscularly. Diuresis is sparing and in the course of three days, complete anuria sets in. The patient dies on the fifth day of peritonitis, paralytic ileus and anuria.

Microscopical examination of the kidneys shows glomerulitis and deposits in several collecting tubules.

It must be supposed, that «Lucosil» has produced a toxic or combined toxic and mechanical intrarenal kidney injury which has been a contributory cause of the lethal course of the illness.

In such an acute infection, it is, however, hard to estimate the part played by the «Lucosil» regarding renal injury.

Facts of Importance Regarding Renal Injury.

As previously stated, a differentiation must be made between the mechanical obstruction of the kidneys and urinary tract, and the toxic injury. So long as the causes of the latter complications are not more precisely known, no directions can be given as to how to avoid them. It should, however, be stressed, that patients who have on one occasion exhibited intolerance towards the sulphonamides, will often have a tendency to develop complications again on renewed sulphonamide administration. This is not only evident from our material but several others, *i. e.* Schnitker (1943), have made similar observations.

It must therefore be recommended that before commencement of sulphonamide therapy, an enquiry should be made as to whether the patient has previously developed complications under sulphon-

amide treatment, and if in the affirmative, this treatment should be omitted, and penicillin be used in its place.

As regards mechanical complications, there are mainly three facts of importance:

The volume of the diuresis.

The reaction of the urine, and

The particular sulphonamide administered.

That the danger of mechanical precipitation decreases with increase in the diuresis, needs no documentation. Even with abundant diuresis, the sulphonamides usually employed will be present in the urine to supersaturation. If the fluid administration be experimentally reduced, there is a sharp rise in the number of kidney complications, as shown by Brown, Thornton and Wilson (1940). The same is naturally the case, if the fluid-balance is upset, owing to repeated vomiting or if the patient perspires freely.

To arrange for the maintenance of an abundant diuresis during sulphonamide therapy is of fundamental importance, and it should be regarded as a dereliction of professional duty to refrain from instructing the patient to drink copiously during the treatment. When the treatment takes place in a hospital ward, the diuresis should be measured and a great effort should be made to prevent this being under 1,500 ml *per diem*. If the patient is in no condition to drink a sufficient quantity, parenteral fluid-treatment should be given.

There has been some discussion regarding the value of alkali treatment as a prophylactic. Alkali treatment might be expected to be logical because the solubility of the sulphonamides is increased with rising alkalinity.

As an example, we give the solubility of sulphathiazole in urine as 17 mg/100 ml at pH 5.5–6 and 187 mg/100 ml at pH 8 (37° C). For acetylsulphathiazole, the corresponding values are 10 mg/100 ml and 265 mg/100 ml.

Against the routine use of alkali is the fact that the alkalis increase the precipitation of sulphonamides in the urine by suppressing their reabsorption in the tubules as shown by Beyer and collaborators (1944). Furthermore, the solubility of sulphathiazole and sulphapyridine shows no striking increase on increase of pH, before approaching the physiological limit of the ability of the kidney to secrete alkaline urine. This limit is for the human kidney, at a pH value of 8.2.

When concerned, however, with the newer sulphonamides, such as sulphadiazine (sulphanilamidopyrimidine), sulphamerazine (sulphanilamidomethylpyrimidine) and sulphametazine (sulphanilamidodimethylpyrimidine), their solubility is increased, also for the acetylated compounds, with reactions already about neutral points.

Clinical investigations definitely suggest that alkali treatment does give results. Schwartz and collaborators (1941), found that alkali administration reduced the number of urines containing sulphonamide crystals in sulphathiazole as well as sulphadiazine treated patients.

Gilligan and colleagues (1943) found that the urine of patients treated with sulphadiazine was nearly always acid, and that 27 % of these patients had crystals in their urine.

On administration of sodium bicarbonate 2.5 g six times a day, the urine of practically all the patients could be made neutral or slightly alkaline. Observation of 350 alkali-treated patients showed no renal damage or crystals in the urine during sulphadiazine administration.

Penna and Christopher (1946) have shown that intravenous injection of 7.5 g sodium bicarbonate in 100 ml water, can make the urine alkaline in the course of half-an-hour, and that injection of this dose twice *per diem*, can prevent the appearance of crystals in the urine. Finally, it has been shown by Murphy and Wood (1943), that there is a relation between the degree of acidity and the quantity of crystals in the urine.

The question of whether alkali should be regularly used under sulphonamide therapy can be debated. Such treatment would probably be difficult to accomplish, especially when dealing with out-patients, but it is absolutely certain that in cases where oliguria and microscopic hematuria are present, alkali treatment should be introduced. Microscopic hematuria appears relatively frequently during sulphonamide therapy and usually progresses benignly. Microscopic hematuria is not therefore a contra-indication for continued treatment, but if there is macroscopic hematuria, it should be instantly stopped.

It should, furthermore, be pointed out, that great reserve should be shown regarding doses of sulphonamide to patients with reduced kidney function. Also, infected kidneys with detritus, which offer points for crystal formation in the supersaturated urine, are a source of danger during intensesulphonamide treatment.

It should, furthermore, be stated that more recent investigations (Seudi and Jellinek, 1943) suggest that in the liver the sulphonamides undergo a partial combining with glucuronic acid or alkylsulphate, whereby a certain fraction becomes soluble in water. This process is reduced in patients with diseases of the liver, and therefore excrete a larger portion of the sulphonamides as the fraction insoluble in water, thus increasing the danger of concretions in the kidneys. In accordance with this, Peterson, Deutch and Finland (1943), found that the frequency of kidney complication during sulphonamide therapy is high amongst patients with diseases of the liver.

The choice of the particular sulphonamide naturally plays an important part in determining the frequency of kidney injuries.

The readily soluble sulphanilamide has, as far as is known, never been the cause of complication, but its relatively slight field of action makes sulphanilamide unsuitable for the treatment of other than streptococcal infections.

«Lincosil» is also readily soluble, but elimination occurs so rapidly, that a therapeutically safe blood concentration cannot be maintained by the usual doses.

Readily soluble sulphonamide compounds of the «Alfasol» type, are converted to a great extent, in the organism, to sulphathiazole, and the risk of kidney deposits is hardly any less on administration of these compounds.

The most recent sulphapyridine compounds, especially sulphamerazine and sulphametazine, are considered to be a vast improvement, both because the «free» compounds are relatively easily soluble, and chiefly because the acetyl derivatives are even more readily soluble, also because the solubility is greatly increased even on slight change in the pH of the urine to the alkaline side.

The best contribution to the solution of the problem has certainly been made by Hagerman (1944). This author has shown that a mixture of different sulphonamides can be present in a solution without the compounds mutually reducing each other's solubility. When applying «The principle of sulpham combinations» one can ensure an effective blood concentration with a minimum danger of the precipitation of sulphonamide crystals in the urinary tract. The preparation he recommended is «Sulfadital» containing, per tablet, 0.37 g sulphathiazole, 0.37 g sulphapyridine and 0.26 g sulphamethylpyrimidine.

This preparation has been clinically tested and appears to have

fulfilled expectations (Frisk and Collab., 1946). It must be hoped that a similar preparation may be introduced in this Country.

The treatment of manifest anuria depends on the type of renal injury. In mechanical extrarenal anuria, ureter catheterisation with mechanical removal of the crystals, and irrigation with isotonic sodium bicarbonate, will, combined with parenteral bicarbonate administration, nearly always lead to success.

The treatment of mechanical intrarenal and toxic anuria is considerably more difficult. Opinions regarding the correct line of treatment are divided, and our material is too scanty to enable us on its basis to propose any therapeutical indications.

It is only reasonable that Mersalyl is contraindicated. Parenteral fluid administration, especially regarding sodium bicarbonate, is recommended by the majority of authors, but when total anuria is present, great care should be taken not to give too large a quantity of fluid to avoid the occurrence of general and pulmonary oedema.

Attention should be drawn to the fact that Lehr (1944) in experiments on rats, found that a dosage of a mixture of sodium bicarbonate 3.3 % and ammonium chloride 1.67 % had a considerably greater effect than a dose of sodium bicarbonate alone. We have here, undoubtedly, a field which deserves closer consideration.

Other therapeutic methods are high lumbar anaesthesia, lumbar sympathetic blockage, and intravenous procain injections (Friis 1946). Decapsulation of the kidney seems to be indicated in certain cases of toxic anuria where there is pronounced oedema of the interstitial kidney tissue.

Finally, we would like to mention that in America, a drastic form of treatment has been conducted with success, and consists of a prolonged perfusion of the peritoneal cavity, with 20—35 litres of Tyrode solution containing glucose, heparin and penicillin (Frank, Seligman and Fine, 1946).

In several cases this treatment has been found to relieve the uremia, and to keep the patient alive until urinary production is fully re-established.

Summary.

A survey of the frequency of renal complications in sulphonamide treatment is given.

The various forms of complications may be divided into the following groups:

- 1) mechanical extrarenal,
- 2) mechanical intrarenal,
- 3) toxic intrarenal.

An account of our own material is given.

During 18 months the following cases have been treated at Bispebjerg Hospital: 7 cases of mechanical extrarenal anuria, 1 case of mechanical intrarenal and 2 cases of toxic intrarenal anuria and, furthermore, 1 of presumed toxic intrarenal anuria. All the 7 cases of mechanical extrarenal anuria were cured. The patient suffering from mechanical intrarenal anuria died. The 2 cases of toxic intrarenal anuria appeared in the same patient at 6 months' interval and proved fatal. The case of presumed toxic intrarenal anuria had likewise a fatal course.

The prophylaxis is discussed and the importance of ample fluid administration during sulphonamide treatment is emphasized; mention is made of the value of alkali treatment.

Finally, a survey of the treatment of sulphonamide anuria is given.

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The Relation of Glycosuria in Pregnancy to Chronic Pancreatitis.

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Introduction.

Although pregnancy is a physiologic phenomenon it puts a considerable burden on the constitution of the expectant mother. That is the reason why during pregnancy ailments existing in a latent state, and new ailments are arising or those which already exist become aggravated.

Therefore the nongynecologic ailments of an expectant mother should be a subject of interest to both the gynecologist and practitioner of other speciality. That thesis is upheld by the monography on diseases of pregnant women published by Professor H. Vignes and his pupils (1935).

In that work a special chapter is devoted to the pancreas, and attention is primarily given to the importance of Glycosuria gravidarum and its connection with diabetes and pre-diabetic conditions (M. Labbé and M. Chevki).

In his work H. Vignes devoted considerable space to acute pancreatitis during pregnancy, and gave full descriptions of the few cases so far mentioned in world literature.

As regards chronic pancreatitis during pregnancy he merely mentions that several authors attempted to explain the disturbances in digestive organs and pains centred in the epigastrium

by the presence of chronic pancreatitis. H. Vignes refers solely to the works of Prochownik in 1915.

It is seen from the aforesaid that the problem of chronic pancreatitis in pregnancy has not yet been fully elucidated.

In the literature accessible to me within recent years I have not found a single description of that disease during pregnancy. Thus my works on that subject in 1940 and 1941 might be considered as one of the first attempts in that line.

However, as seen from the works of numerous authors, the matter of the functioning of pancreas during pregnancy has been investigated for a long time past. Those researches have proved that during pregnancy disturbances both in internal and external secretion can be found. As evidence of that statement I shall quote only a few of the fairly numerous works of various authors.

External Secretion.

As far back as 1921, Cantoni proved that during pregnancy the lipase and trypsin shown in duodenal contents are temporarily decreasing. Besides that, numerous experiments were made on the condition of diastase in the blood and urine of pregnant women. The majority of experiments show the increase of that ferment in the urine (F. Eckardt — 1935).

Within recent years a special attention has been devoted to diastase in blood during pregnancy. Thus, for instance, Marzetti (1934) ascertained the increase of diastase in blood during the period of pregnancy. He tries to explain that phenomenon by the action of three factors: hyperfunction of the pancreas of the mother, the increased activity of the foetus starting from the second half of the period of pregnancy, and the hindrance of the outflow of pancreatic juice from mother's pancreas.

Internal Secretion.

It has been known for a long time past that Glycosuria occurs often during pregnancy, and that this phenomenon is more frequently detectable after carbohydrate ingestion.

Payer has demonstrated as far back as 1899 that after an ingestion of 50 grams of glucose Glycosuria appears in 50 % of cases during pregnancy. Reichenstein of the Professor Gluzinski, Lvov

Clinic in 1909 detected Glycosuria after ingestion of glucose in 38.3 % of cases of pregnancy. (In 27.6 % of cases sugar in urine appeared in considerable quantity, and traces of sugar in 10.7 % of cases.) Within recent years M. Labbé and M. Chevki (1926) have proved that after ingestion of 50 grams of glucose 10 pregnant women out of 37 had sugar in urine, while the morning urine on fasting showed sugar in one case only out of 10 women examined. Further, M. Labbé and M. Chevki have demonstrated that in the course of pregnancy irregularities in the blood sugar curve (prædiabetes) may be observed fairly often, and that Glycosuria in pregnancy appears as a result of a temporary lowering of the renal threshold.

The above data are an entirely sufficient proof of appearance of disturbances in the functions of pancreas during pregnancy, but do not explain the reason of such disturbances. Those data do not furnish sufficient grounds for deducing whether the functions of that organ have been only temporarily disturbed during pregnancy, or that the mentioned symptoms are accompanied by deeper anatomic changes which were present prior to pregnancy or developed during it and were detected through the discovered disturbances of the pancreas. Thus, when considering the importance of Glycosuria in pregnancy, the physicians could do no more than to differentiate whether they were confronted in the respective case with: 1) Glycosuria renalis gravidarum, or 2) Diabetes mellitus of a higher or lower degree. I dealt with this matter at length in my work of 1933 on the basis of a selected literature and numerous personal observations. It was difficult to speak then of the closer participation of the pancreas in abnormal cases, particularly of a chronic inflammation of that organ, because until recently our methods of examination were insufficient in that respect. This applies particularly to the latent forms of chronic pancreatitis difficult to detect.

Until 1935 the methods used for research enabled to detect chronic pancreatitis only in such cases in which the symptoms were quite obvious, *i. e.* in the stage of disease correspondingly advanced. I have not, however, met such cases among women showing Glycosuria during pregnancy. From the time of inventing my own method of palpatory examination of the pancreas, which method I have described in 1935, the chances of detecting the early stages of chronic pancreatitis improved considerably. Thanks to this, I was able to work out in 1935 and 1936 my own system of

detecting the latent forms of chronic pancreatitis. I brought all data on that matter to public notice in my latest works.

That system consisted in applying a better understanding of a normal and diseased functioning of the pancreas. On the basis of my aforesaid works and those published later, I am devoting particular attention, during my examination of the patient in each case, to the anamnesis which may have connection with the pancreas. For it must be borne in mind that ailments of adjacent organs (liver, stomach, duodenum) very often cause a diseased condition of the pancreas. Therefore in the anamnesis I devote my attention to such symptoms as general weakness, sudden loss of weight, thirst, pruritus, abundance of saliva, temporary glycosuria and the condition of teeth.

Further, irrespective of ascertaining the above mentioned complaints, I perform a systematic physical examination of the pancreas of every patient. I examine in the pancreas region the following:

- 1) hyperesthesia,
- 2) trophic changes in the skin, *i. e.* changes in the nutrition of the skin (J. W. Grott, 1937),
- 3) degree of pain in the point of crossing of the pancreas with the vertebral column («point douloureux» for pancreas body — J. W. Grott, 1935),
- 4) I test by my method¹ whether it becomes possible to ascertain an enlargement of the pancreas.

Besides, I am thoroughly examining the teeth, looking for changes in the form of receding gums or shaking of the teeth.²

The appearance of one or several of the above symptoms would give an important proof of participation of the pancreas in the disease, necessitating the making of special laboratory tests indispensable for giving a more precise diagnosis.

Those tests should comprise:

- 1) Testing of urine for sugar contents after ingestion of 50 grams of glucose and still better the fixing of blood sugar curve,

¹ A palpatory examination of the pancreas is feasible in the first half of the period of pregnancy only.

² I mean primarily the symptoms of paradontose (J. W. Grott 1) Polish Archives of Internal Medicine, 1937, No. 2; 2) Polish Medical Gazetto, 1937, Nr. 16, 3) Gastroenterologia, 1941; volume 66, No. 2; and 4) Die Bedeutung der Paradontose als wichtiges Symptom der Frühdiagnose der Diabetes: a) Schweiz. Med. Wschrift, 1942, p. 1249, and b) Nowiny Lekarskie, 1946, No. 23 (in polish).

2) Testing the diastase in the morning urine and in that released after my test breakfast,¹

3) The stools examination after 3 days of diet modified by me (J. W. Grott, a) Polish Archives of Internal Medicine, No. 2, 1935, b) Arch. App. Dig. 1939, No. 1).

It results from the above that the clinical examination of the pancreas is a rather complicated process, thanks to which the modern diagnosis would be based not on one symptom only but on a syndrom obtained from the complex of all the results derived from anamnesis, physical examinations and laboratory tests.

It should be mentioned further that as far back as 1936 I demonstrated in my work on carbohydrate metabolism in the pancreas diseases that:

1) In chronic pancreatitis may appear very low blood sugar curves showing that the morbid condition may be accompanied by a possible hyperfunction of Langerhans islets;²

2) In chronic pancreatitis the Glycosuria renalis appears fairly often,

3) The low blood sugar curve and Glycosuria renalis may completely disappear at the improvement in the ailment.

It results that Glycosuria renalis, a symptom hitherto considered as a very characteristic feature of pregnancy may be simultaneously a symptom frequently appearing in chronic pancreatitis.

My Own Researches.³

In view of such results of my own researches on pancreas diseases, a question arises regarding the functioning of the pancreas during pregnancy, especially in cases showing Glycosuria, and whether it might be possible to prove, at least in some cases, that

¹ The Test breakfast suggested by me consists of 30 grams of oatmeal boiled in water and served with butter, 40 grams of biscuits and 20 grams of butter (J. W. Grott, a) Pol. Arch. Med. Wew. 1935, No. 2 and b) Gastroenterologia, 1939, Vol. 64, fasc. 2—3).

² For further particulars see: J. W. Grott »Chronische Bauchspeicheldrüsenerkrankung mit Hyperfunktion der Langerhans'schen Inseln«, Gastroenterologia, Vol. 66, fasc. 2 (1941).

³ Because of lack of space in the present study, I am discussing solely the results of summary examinations. I gave the description of interesting cases in my former works. J. W. Grott: 1) Monatschrift für Geburtshilfe und Gynäkologie 1941, Vol. 112, fasc. 2, and 2) Acta Med. Scand. 1941, fasc. 1, page 80, 3) Rinnascenza Medica, 1940, No. 16, 4) Schweiz. Med. Wschrift, 1941, No. 32, page 930, 5) Nowiny Lekarskie (Medical News), 1946, No. 8, page 145.

Glycosuria is one of the symptoms of chronic pancreatitis in the course of pregnancy.

Realizing the obstacles caused by pregnancy itself, I devoted a special attention to that matter. The data collected by me in recent years concern 50 women who showed Glycosuria during pregnancy at the time of examination or previously. In accordance with this point I classified my women patients into three groups according to diagnosis.

The first Group comprises 11 women who had Glycosuria gravidarum without any symptoms of chronic pancreatitis during pregnancy or after its termination. 20 women with chronic pancreatitis, ascertained or very probable, during pregnancy I classified in Group II. Finally, in Group III I deal with 19 women who suffered previously of Glycosuria during pregnancy and who are undoubtedly suffering from diabetes.

In all these cases I tried to carry out my researches in accordance with the aforesaid pattern, but because of circumstance it was not always possible to do it to the full extent.

Description of Result of Researches.

Group I.

Glycosuria Gravidarum without Symptoms of Pancreatitis.

In this group 11 women were medically examined of whom 6 (subdivision A, persons Nos. 1—6) showed glycosuria in pregnancy at the time of examination, and the other 5 women (subdivision B) had sugar in urine during their previous pregnancy. Of those one (No. 7, M. S.) was in her second pregnancy. The patients of subdivision A had sugar in various degrees in their urine (No. 1, P. L. — 0.5 %, No. 2, K. R. — 0.7 %, No. 3, J. R. — 1 %, No. 4, K. D. — 5.6 %, No. 5, A. P. — 1 %, No. 6, H. W. — 3 %). Two of them complained of pruritis in the arch of the pubis (Nos. 3 and 4). No. 5, A. P. — of unexplainable fatigue, and the patient No. 6, H. W. — of unpleasant flow of saliva which she did not have before. Physical examination showed a very marked hyperaesthesia in the pancreas region in one case only, that of No. 2, K. R.

Only three patients (Nos. 1, 2 and 4) agreed to undergo laboratory tests. For the diastase examined in the morning urine and after the test breakfast, the results were as follows: Patient No. 1 — 200/200 Wohlgemuth units, No. 2 — 100/100, No. 4 — 25/25.¹

¹ Diastase in urine has been tested by 24 hours Wohlgemuth method.

As regards the sugar blood curve, as shown on Table 1, it has been very low in cases Nos. 1 and 2, and in case No. 4 it showed slight irregularities.

Table No. 1.

Behaviour of blood sugar curves after ingestion of 50 grams of glucose.

Time	0'	45'	60'	90'	120'	180'	Glycosuria in % after		
							1 hour	2 hours	3 hours
No. I/V ¹	73	99	86	99	79	50	0.5	trace	0
No. 1/VII.....	60	90	—	58	44	60	1.0	(—)	1.4
No. 2/VIII.....	77	123	119	111	98	63	0.5	0.7	0
No. 4/VII.....	97	187	125	134	129	90	2.3	4.7	2.5

It is characteristic that in case No. 1 as seen from the comparison of the blood sugar level in the fifth and seventh month of pregnancy, with the advance of pregnancy the degree of sugar in blood, and simultaneously the renal threshold, became considerably lower. This proves the increase of the percentage of sugar in the second examination.

In the five cases of subdivision B in which previously glycosuria in pregnancy was detected — that symptom does not appear, and no disease of the pancreas could be detected. Thus, it is characteristic that in case No. 10, Z. D. (Table No. 2) although the results of the tests of the blood sugar curve during pregnancy and at the present time were the same, yet after the end of pregnancy the renal glycosuria does not appear any longer.

Table No. 2.

Blood sugar curve of patient No. 10 — Z. D. during the eighth month of pregnancy (I — 29th May, 1929) and four years later (II — 19th March, 1933).

Time	0'	45'	60'	90'	120'	180'	Glycosuria in % after		
							1 hour	2 hours	3 hours
I.....	87	134	117	131	102	79	0.2	0.6	0.2
II.....	100	137	131	134	67	84	—	—	—

The above data concerning 11 cases of glycosuria in pregnancy lead to the conclusion that although those women showed individ-

¹ Month of pregnancy.

² Not examined (—).

ual symptoms appearing fairly frequently in chronic pancreatitis, yet the mentioned data is not sufficient to make a diagnosis to that effect.

It should be mentioned, however, that in case of patients of that group there existed, besides the difficulty of diagnosing a chronic pancreatitis, other considerable difficulties in detecting a disease of the pancreas in patients examined after a lapse of a long time after the end of pregnancy. There is always a possibility of disappearance of symptoms as result of improvement or natural cure.

Group II.

Glycosuria Gravidarum with Symptoms of Chronic Pancreatitis.

To the second Group belong 20 women in the case of which chronic pancreatitis could be ascertained quite positively or most probably on the strength of examination and tests.

Of those patients, only 12 (subdivision A) were pregnant at the time of examination, and the remaining 8 (subdivision B) had before an ascertained glycosuria in pregnancy, and are now being treated for chronic pancreatitis.

Subdivision A.

This group comprises 12 persons (Nos. 12—20, and 47, 48, 49). This is a group of the greatest importance in my work for it furnishes a positive proof that in the course of pregnancy the chronic pancreatitis occurs fairly often.

Discussion of Cases.

As a result of enquiries made to patients, the following main symptoms should be noted: bad general psychic and physical condition, then symptoms of indigestion, and above all the inclination to constipation, a feeling of thirst (8 in 12 cases, Nos. 11 — J. F., 12 — E. T., 16 — D. T., 17 — J. P., 20 — J. Sz., 47 — R. M., 48 — Z. St., 49 — S. Ska) and finally pains in the left side in three cases, *i. e.* $\frac{1}{4}$ of the total number of cases (Nos. 12, 13 and 16).

A very marked skin hyperaesthesia in the pancreas region has been found in 4 cases of 12 ($\frac{1}{3}$ of cases — 33 %).

As regards trophic changes in the skin of the pancreas region, I have discovered that symptom only recently and have described it, and could consequently examine it on some patients only, on those who applied to me at the last stage of my writing this study.

I found this symptom in 6 cases out of seven medically examined (Nos. 12, 19, 20, 47, 48 and 49) and I may say that I found changes in the nutrition of the skin during pregnancy in 4 cases only (Nos. 19, 47, 48 and 49), whereas in the remaining 2 cases I discovered the changes in the skin during further examinations, after childbirth (No. 12, E. T. three years after, and No. 20, J. Sz. 4 weeks after childbirth). Nevertheless the percentage is very high (59.1 %) which fact merely enhances the practical value of that symptom described by me.

But the most interesting results were obtained by palpatory examination of the pancreas by my own method. The painfulness of the vicinity of pancreas body I succeeded in tracing in 9 patients who were in the first half of the pregnancy period. That test was impossible in the remaining cases (Nos. 10, 20 and 47) because of their advanced stage of pregnancy (8th and 9th month). I may mention that in cases Nos. 15 and 16 at the beginning of the 6th month of pregnancy the palpatory examination of the pancreas was still possible, though difficult.

As mentioned, in the case No. 20, J. Sz. the ninth month of pregnancy formed an obstacle for making the test, but in the fourth week after childbirth it became easily possible to find a palpatory painfulness of the pancreas. On examination of Mrs. Rose M. (No. 47) four months after confinement I found the pancreas increased in form of a cylindrical body which was fairly painful.

These observations form a proof of the fact that when because of advanced pregnancy there are obstacles to a palpatory examination of the pancreas, such examination should necessarily be made after childbirth. It should also be mentioned that in four cases of pregnancy I was able to ascertain an increase of the pancreas body in a shape of a painful cylindrical body (Nos. 14, 15, 17 and 49).

Besides the physical examination of the pancreas, laboratory tests proved very useful, primarily the testing of diastase in the morning urine and after the test-breakfast, and the examination of blood sugar curve and glycosuria after the ingestion of 50 grams of glucose. The testing of stools after test diet made with a certain number of patients enabled the detection of slight difference from the normal in some cases only.

The blood sugar curve after glucose was examined in 11 cases of the 12 under consideration. Solely in the case of one patient R. M. (No. 47) the disturbances in carbohydrate changes were

greater, so that a mild form of diabetes developed slowly and gradually.¹

The rest of the patients showed before breakfast a normal blood sugar level, although with a considerable margin (from 56 to 111 milligrams%). The heights of the blood sugar curves after 45—60 minutes reached in the case of seven patients 160 mg. One patient (J. P. No. 17) was an exception, for the height of her blood sugar curve reached 226 mg, but after an appropriate treatment the disturbances in the curve were soon eliminated.

Generally, as most frequent irregularities in carbohydrate changes in that group of patients noticed by me were the delays in return to normality of the blood sugar curve after 90—120 minutes.

Valuable data have also been obtained from the examination of diastase in urine. Although the regular behaviour of that substance in the urine does not exclude a possibility of pancreas disease, yet it is worth while to carry out that examination, for an increase of diastase forms an undoubtful indication of the existence of disturbances in that organ.

I have discussed at length this matter in a special work, in which I upheld the correctness of such point of view.²

Thus of the 11 patients examined, 5 (Nos. 11, 12, 13, 20, 49), *i. e.* almost a half (exactly 45.45 %) have shown large quantities of diastase (200 W. units and more) in urine, 4 showed fairly large (100 W. u.) and only 2 — normal, *i. e.* not exceeding 50 W. u. The above figures prove the high practical importance of examination of the diastase in urine of patients of that category.

The high percentage of positive results, *i. e.* high (100 W. u.) and very high (200 W. u. up) may be explained by the fact that pancreatitis in pregnancy is a relatively new phenomenon, or that during pregnancy it became acute or reappeared again. This would be in accordance with a well-known fact that the possibilities of detecting diastase in urine are dependent on the acuteness of the pancreas disease or of the recent date of aggravation of an old disease.

In the present discussion of cases I restrict myself solely to the most important data. It results incontestably from precise consideration of a total clinical examination in each individual case that all the 12 patients suffered of great disturbances in the pancreas caused most likely by chronic pancreatitis.

¹ This case is rare and interesting. I described it separately (J. W. Grott: *Rinascenza Medica*, 1940, No. 16, and in *Nowiny Lekarskie* (Medical News) 1946, No. 8, page 145.

² J. W. Grott: Diagnostic importance of diastase in urine in the diseases of pancreas (*Medycyna*, 1937, No. 8).

Subgroup B.

This group comprises observations concerning 8 women who showed Glycosuria in pregnancy, and in whom later a chronic pancreatitis was found. In three cases examinations were made within a year after confinement (No. 21, M. M. — 4 weeks after childbirth, No. 22, J. E. — 3 months, No. 23, J. B. — 12 months) and in the case of the remaining 5 patients considerably later (No. 24, M. M. after a lapse of 4 and 6 years, No. 25, H. K. after 5 years, No. 26, J. K. — after 7 years, No. 27, Z. L. after 7 and 11 years, and No. 23, M. C. after 3 years.

Discussing the more Important Data.

Enquiries. All of the above mentioned patients had glycosuria during their last pregnancy. At the present time two (Nos. 21 and 22) complain of troublesome nervousness and acute exhaustion both physical and psychic; two (Nos. 21 and 25) complain of constant thirst; one (No. 22) of pains »in the spleen», 5 of recurring glycosuria, and one of itching of the skin.

Physical Examination.

By palpatory examination a painfulness in the vicinity of the pancreas body was found in all the 8 patients, and in 4 (Nos. 21, 22, 23, 25) of them an increase of the pancreas body in the form of a painful roller could be ascertained.

Trophic changes of skin in the pancreas cylindrical body region were examined in 4 patients of whom 3 showed such changes (Nos. 23, 24, 28), but hyperaesthesia was found in one patient only out of 4 examined for that symptom (17 %).

It is characteristic that in the group II A, *i. e.* patients suffering from chronic pancreatitis during pregnancy, hyperaesthesia was found by me twice more often, *i. e.* in 3 of 9 patients, *i. e.* 33 %.

Laboratory Tests.

As regards diastase in urine, out of 7 patients examined 4 showed the level of diastase of 200 and more Wohlgemuth units, 1—100 units, and 2 — not exceeding 50. It results from this that in the majority of cases, *i. e.* 5 out of 7, the diastase was increased which represents a very high percentage of positive results of tests.

Examination of carbohydrate metabolism by means of ingestion of 50 grams of glucose in 7 cases, showed glycosuria in 5. Out of

that number, in 4 cases, except patient No. 23, glycosuria was caused by the lowered renal threshold. It results from this that in the majority of cases (4 out of 5, *i. e.* 80 %) of women who had glycosuria in pregnancy, if they had chronic pancreatitis the glycosuria continued to maintain the character of renal glycosuria.

This is important, for such occurrence may show a connection between the symptom existing now and a similar symptom which existed previously during pregnancy. The feature of that glycosuria in our patients must be particularly underlined, in view of the fact that in 1936, when describing the behaviour of carbohydrate metabolism in chronic pancreatitis, I have proved¹ that kidney glycosuria is occurring frequently in the course of chronic pancreatitis, and that this symptom disappears at the moment of improvement or recovery.

The blood sugar curve after 50 grams of glucose was normal, but in most cases showed some delay in return to normal condition, and only in three cases the highest blood sugar level was slightly higher than 160 mg% (Nos. 21—162, No. 23—199 and No. 24—164 mg%).

Taking into consideration the whole of clinical tests made for those patients, and taking into account the aforesaid reflections, it may be stated that in all those 8 cases chronic pancreatitis could be ascertained. We may also presume the high probability that this pancreatitis is not a newly acquired disease but a continuation of that existing priorly and being detected due to the finding of glycosuria during the last pregnancy.

Group III.

Diabetes of Patients having Glycosuria in Pregnancy.

In Group III I am discussing the results of examination of 19 women affected with diabetes who at a given time in pregnancy had glycosuria only (14 women) or all ill with diabetes which dates since their last pregnancy (5 women).

In view of the fact that the patients suffering from diabetes show often an insufficient external secretion of the pancreas, which symptom has been noted by many authorities,² and as results

¹ J. W. Grott: *Medycyna*, 1936, No. 24.

² A detailed statement of results of studies of various authors concerning the condition of external secretion of the pancreas of sufferers of diabetes is given by A. Puech and P. Rimbaud, *Congrès Français de Médecine*, XXIII Session, Québec 1934. Masson et Cie, Paris, 1934.

from my former examination of patients of that category — as a rule low quantities of diastase in urine are found. I have therefore given my chief attention to the estimate of results of physical examination of the pancreas. I have thus divided all cases in two subdivisions in accordance with the degree of painfulness of the pancreas.

Subgroup A.

Diabetes without Clinical Symptoms of Pancreatitis.

Subgroup A concerns 9 persons of whom 2 (No. 30, St. L. and No. 33, J. L.) had diabetes dating from their last pregnancy, and the remaining 7 contracted this disease in the course from 2 to 20 years after their pregnancy (No. 29, J. Z. — 3 years; No. 31, H. K. — 20 years, No. 32, C. K. — 10 years; No. 34, J. Sw. — $8\frac{1}{2}$ years; No. 35, A. Z. — a few years; No. 36, St. B. — 2 years, No. 50, H. — 15 years.)

In all those 9 patients I did not succeed once in detecting painfulness of the pancreas or hyperaesthesia in the pancreas region. I neither found any trophic changes of the skin in the 5 patients examined. Diastase in urine was neither increased.

It results from this that the physical examination of the pancreas to which I am inclined to attribute the greatest importance in this category of patients, gave me in 9 sufferers of diabetes of this group no sufficient background for diagnosis of chronic pancreatitis at this time. There was no possibility therefore to connect precisely their present diabetes with a possible disease of the pancreas during pregnancy. Yet those patients had undoubtedly a mild and concealed form of pancreatitis which could be detected in pregnancy thanks to the appearance of glycosuria, and that the pancreatitis existing for a long time without any symptoms finally brought about diabetes.

Subgroup B.

Diabetes with Symptoms of Chronic Pancreatitis.

In the Group III, subgroup B concerns 10 women ill with diabetes of whom three (No. 41, T. F.; No. 42, J. R. and No. 44, A. Sw.) got diabetes after their last pregnancy, and the remaining 7 developed diabetes later, within 1 to 7 years (No. 37, Cz. B. — 1 year; No. 38, M. W. — 7 years; No. 39, B. S. — 6 years; No. 40, B. B. — 2 years; No. 43, M. W. — 3 years; No. 45, M. B. — 6, and No. 46, E. Z. — 4 years.)

In comparison with subgroup A diabetes appeared here much earlier, if counting the time of its detection in relation to pregnancy connected with glycosuria.

All those 10 patients manifested considerable painfulness of the pancreas, and further in 5 patients (No. 39, 40, 42, 44 and 46) the pancreas could be detected as a cylindrical and painful body.

Hyperaesthesia of the skin appeared only in one of the 4 patients examined. Trophic changes of the skin in the pancreas region were found in all of the 3 patients examined in that respect. The diastase of the urine was not increased.

Reassuming the above data we reach the conclusion that in this group of patients, chronic pancreatitis very probably existed simultaneously with diabetes. Besides the aforesaid data, another important factor for diagnosis was in many cases the very characteristic data obtained by examination of individual cases, either by enquiries, results of clinical tests repeatedly made, or by results of treatment. The importance of steady observation of the patient by the same physician should be emphasized. By treating my patients during a number of years I had frequently the possibility of noticing how the symptoms of painfulness of the pancreas detected by palpatory examination were appearing in cases of aggravation of the disease caused, for instance, by infection of faulty diet, and how that painfulness was disappearing when an improvement was occurring.

Regarding all the 19 cases of Group III, we may conclude that in 10 cases, *i. e.* 55.55 % it became possible to detect the simultaneous appearance of chronic pancreatitis and diabetes.

It results therefrom that in at least one half of the number of diabetic patients, *i. e.* of those who once had glycosuria in pregnancy, the present diabetes and chronic pancreatitis may be connected with a previous pancreas disease which occurred during pregnancy.

Conclusion.

In the present work I have discussed the results of examination of the pancreas in 50 women patients who had glycosuria in the course of or after pregnancy. The results obtained are shown in table No. 3 enclosed.

From a thorough examination of the data given it appears that in 24 % (12 persons) of the number of women examined it was possible to detect symptoms indicating a chronic pancreatitis

during pregnancy. In 18 women (36 %) symptoms of chronic pancreatitis were detected only in later examinations, after a lapse of a longer or shorter period of time after pregnancy during which glycosuria has been detected. Thus, in 12 women precisely and in 18 indirectly it became possible to connect the glycosuria, detected during pregnancy, with a disease of the pancreas. That represents a very high percentage, namely 60 %.

Table No. 3.

Glycosuria in pregnancy	Persons	Recognised symptoms of chronic pancreatitis		
		pregnant	after pregnancy	Total
I. Without symptoms of pancreatitis	11	—	—	—
II. With symptoms of pancreatitis	20	12	8	20
III. In sufferers of diabetes ...	19	—	10	10
Total number of persons	50	12 (24 %)	18 (36 %)	30 (60 %)

The above figures are very valuable, for they confirm once more the correctness of the deductions of my former works, *i. e.* that in every case of pregnancy occurring with glycosuria it is necessary to examine systematically the pancreas by methods described by me. This applies particularly to the period of the first half of pregnancy, and to the period after confinement.

The obtained proportion of 60 % of cases showing the connection of glycosuria in pregnancy with pancreatitis which existed during or after pregnancy is perhaps too high. The reason of that may be the limitation of material of research which was merely 50 cases. The exact situation may be established by subsequent researches embracing a vaster material. Nevertheless, the present work might be considered a factor of some importance, for it implies that the subject of renal glycosuria may be an interesting field for subsequent clinical examinations of the reaction of pancreas in pregnancy.

This would be still more desirable in view of the fact that as far back as 1936 I devoted an exhaustive study to the carbohydrate metabolism in pancreatitis. I have proved that renal glycosuria is a frequent symptom of chronic pancreatitis.

Besides, as I am proving in the present study, if a woman had

glycosuria in pregnancy, and a chronic pancreatitis was detected in her later on, then in 80 % of such cases such glycosuria has a character of renal glycosuria. It appears therefore that renal glycosuria may occur not only during pregnancy, but it forms very often an important symptom in the course of chronic pancreatitis.

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From the State Bacteriologic Laboratory, Stockholm.

Primary Atypical Pneumonia.

A Report of 112 Cases with a positive Cold Agglutination Reaction.

By

GUNNAR LAURELL.

(Submitted for publication August 4, 1947.)

Introduction.

Primary atypical pneumonia is an acute infectious disease in the respiratory tract. It has been especially studied in U. S. A. and England during the past few years. There is, however, no reason for assuming that it is a new disease; it has without doubt existed for many years in other countries also, among them Europe. As far back as 1918, Clough and Richter (6) described a couple of typical cases, and in 1935 a fairly large epidemic was reported by Bowen (3) from a military camp at Hawai. A fairly extensive epidemic was also described by Reimann in 1938 (22). In England, the disease was observed by Scadding and Ramsay (25, 26) in 1937. The first fairly exhaustive description of it was furnished by Kneeland and Smetana (17) and by Longcope (18), in 1940. During the War, it was very common among soldiers both on active service and in training camps, and in connection with these epidemics a number of publications have appeared giving detailed reports both on the clinical picture and the etiology of the disease (2, 8, 9, 10, 11, 12, 19, 21, 23, 24, 31, 32, 33, 34, 35).

In Scandinavia, the disease was first mentioned in Sweden in the spring of 1945 (15), and since then several authors have published papers on it, from Denmark, among other countries

(1, 16, 27, 28, 29, 30). The disease has previously been known under a variety of different names, such as interstitial pneumonia, pneumonitis, virus pneumonia, and others. The name now generally accepted in U. S. A. is primary atypical pneumonia. The term often used in Sweden, virus pneumonia, cannot be regarded as adequate, as, in the first place, the disease is presumably caused by several different infecting agents, and in the second place, none of these has yet been demonstrated with certainty. According to Horsfall (14), it is also possible that the disease is due to a synergy between virus and bacteria, a so-called complex infection.

Judging by earlier American investigations the opinion held was that the disease constituted, from the clinical aspect, a relatively uniform group, but in later publications an ever increasing number of authors are abandoning this view. In one of the latest articles, for instance, the Commission of Acute Respiratory Disease (4) asserts that »atypical pneumonia may be one disease or it may be several diseases; it may be produced by one agent or by many agents; it may have only one clinical form or it may vary from the mildest of infections of the upper respiratory tract to the most severe and fatal pneumonia; it may spread only by direct and intimate contact with cases and carriers, or it may be air-borne in the truest sense».

Material.

My material consisted of patients with suspected primary atypical pneumonia from whom blood samples for the estimating of cold agglutinins had been sent to the State Bacteriologic Laboratory. In 112 cases the reaction was positive and only these cases were included in the present investigation, as the object was to obtain as homogeneous a material as possible. This does not mean, however, that clinically typical cases with a negative reaction could not have been primary atypical pneumonia. The cold agglutination test was considered positive when, from having been negative in serum taken during the acute phase of the disease, it was positive in the convalescent stage with a titer of at least $1/8$ — $1/16$. The same was the case if the titer increased during the course of the disease from, for instance $1/4$ to $1/16$. A single value from the convalescent phase of the disease, with a titer of at least $1/16$, was also considered to be sufficient. In American investigations, a borderline titer of $1/16$ is often stated to be

too low. This value was regarded as sufficient in the present investigation, however, since with the method used, only a few sera had a titer of 1/16 or over among a total of 500, consisting of both normal sera and sera from patients with infections of the upper respiratory tract of a different origin.

Methods.

Sputum. The sputum samples examined were kept in a frozen state at -70° C. In the examinations for virus, sputum samples were obtained during the acute stage of the disease and were frozen as soon as possible, as a rule not later than a couple of hours after they had been obtained. Pulmonary tissue from the only patient who died was also preserved in the same way.

Culture medium. In the examination of the ordinary throat flora a blood agar plate with 10 per cent blood was used. This was incubated in a thermostat for 24 hours at 37° C. and analyzed for α -streptococci, β -streptococci, staphylococcus albus and staphylococcus aureus. In tests for the purpose of demonstrating a specific encapsulated gamma streptococcus the selective medium described by Horsfall et al. (7, 20) was used.

Virus. Sputum samples were ground together with fine sand and broth and were then centrifuged for 10 minutes at 1,500 R. P. M. The only piece of pulmonary tissue examined was treated in the same way. The supernatant fluid obtained after the centrifuging was used for inoculation. Mice and guinea-pigs were used as the experimental animals. These were inoculated intranasally, intracerebrally and intraperitoneally. The animals were killed 7—14 days after the inoculation and submitted to examination. Serial passages were done with a 20 per cent lung suspension from the animals that had been inoculated intranasally.

Cold agglutinins. Wherever possible, blood samples were taken during the first days of illness and again after about 10 days, or during the convalescence. The blood was kept at room temperature until the serum had been separated by centrifugation.

Human O red cells which had been washed twice with physiologic saline were used as antigen in a 1 per cent red cell suspension.

0.3 ml of red cell suspension was added to 0.3 ml of a falling series of serum dilutions (1/2, 1/4, and so on). The dilutions were prepared in physiologic saline, and ordinary Widal tubes were used for the titrations. Readings were made after the tubes had been kept overnight at a temperature of $+5^{\circ}$ C; the readings had to be done immediately after the samples had been brought from the cold-room as the agglutinins become rapidly eluted when kept at a higher temperature. The results were recorded by the same method as that used in Paul-Bunnell's reaction. The reaction is considered as strongly positive (5 plus) when a solid disk which can be shaken up as a firm flake and the positive reactions are then graded according to the durability of the flake in the following manner.

5 plus: The flake can be shaken without falling to pieces.

4 plus: The flake breaks up into large fragments.

3 plus: The flake breaks up into small fragments readily distinguishable with the naked eye.

2 plus: The flake breaks up into small fragments which are just distinguishable with the naked eye.

1 plus: The flake breaks up into very fine fragments which are distinguishable under a magnifying glass. This is counted as a negative reaction.

In the positive samples, the 5 plus reaction often occurs high up in the dilution series while it hardly occurs at all in normal sera, even in the lowest dilutions. The reaction was checked by placing the positive tubes in a thermostat at $+37^{\circ}\text{C}$ for half an hour and then taking another reading. No agglutination should then be found.

Clinical Laboratory Findings.

White blood cells and sedimentation rate. A white cell count and a sedimentation rate according to Westergren, were carried out in every case. The highest white cell counts are shown in table 1.

Table 1.

The highest total white blood cell counts in 112 cases of primary atypical pneumonia.

White blood cells per ml	No. of patients in given range
3,000—6,000	21
6,000—9,000	40
9,000—12,000	28
12,000—15,000	10
15,000—20,000	10
> 20,000	3

In 89 cases the white cell count was normal or only moderately raised during the whole illness. In a few cases, however, especially in patients with a moderately severe or severe form of the disease, a high white cell count was obtained. A feature of interest was that the white cell count often only reached its highest level towards the end of the febrile period. The sedimentation rate was considerably increased in most of the cases, and values of over 100 mm in 1 hour were a not uncommon finding.

Bacteriologic studies. Cultures from sputum made on ordinary blood agar plate yielded a rather various flora of bacteria, the

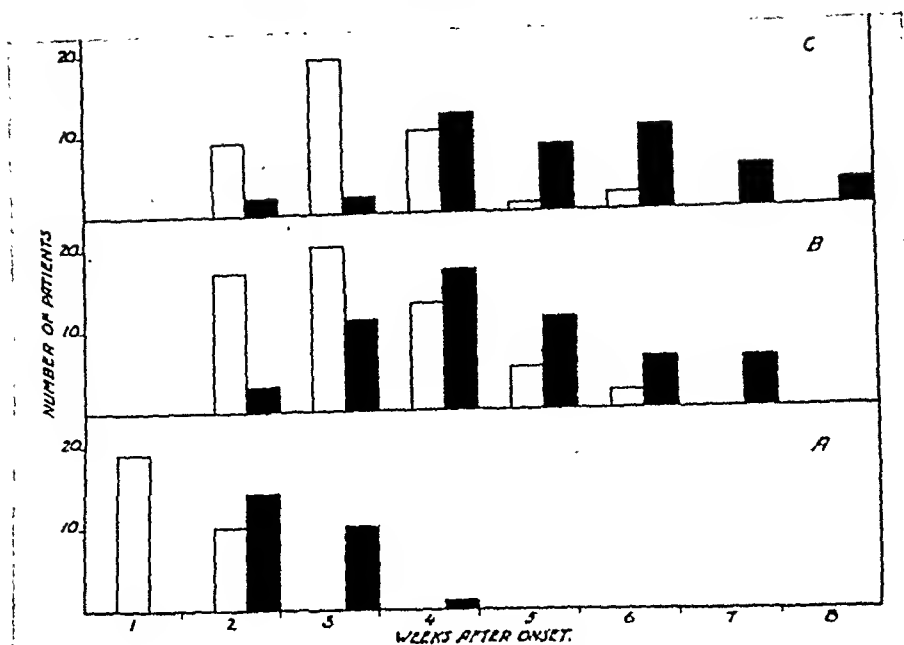


Fig. 1. Time of appearance and disappearance of cold agglutinins in Primary Atypical Pneumonia.

A. First appearance (29 cases): open bars last negative test; solid bars = first positive test.

B. First significant (2 fold or greater) drop in titer (55 cases); open bars = last observation of the maximum titer; solid bars = first test after the drop in titer.

C. Disappearance (41 cases): open bars = last test before a 2 fold or greater drop in titer to 16 or less; solid bars = first test in which the titer was 16 or less (the last of these includes 1 case each on days 56, 63 and 98 respectively).

predominating type being α -streptococci. On the whole, the same bacterial flora was obtained as in healthy individuals. At the clinics where examinations for pneumococci were routinely made, several types, especially those of the higher types, were demonstrated in a number of cases. These do not seem to have played any part in the course of the disease, however.

When Horsfall's special medium was used, an encapsulated streptococcus resembling the MG-streptococcus found by American investigators was demonstrated in only one case.

Virus studies. Attempts were made to detect virus in a few cases. So far, however, all these experiments have had a negative result. In some instances, latent virus types in the experimental animals made it impossible to judge the results. We have not yet performed any tests by the Eaton method, by which preliminary inoculation of the amniotic sac in chick embryos, followed by passage of amniotic fluid to cotton rats, is done.

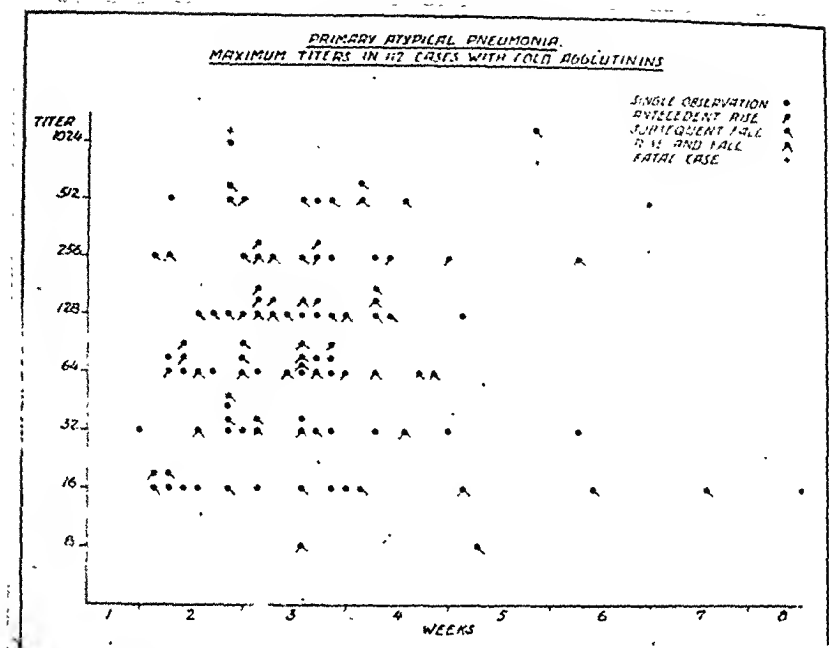


Fig. 2. Each dot represents the maximum titer of cold agglutinins in one patient and the time after the onset of the disease when that titer was first demonstrated. A short line sloping up to a dot from the left indicates that observations of lower titers were made in that case before the maximum titer was obtained. A similar line sloping down to the right from the dot indicates that there were subsequent observations of lower titers. Dots without such lines indicate single observations or multiple observations of the same titer within a brief period.

Serologic studies. Sera from patients taken both during the acute stage and during convalescence were tested by slide agglutination against the encapsulated α -streptococcus that was found. Agglutinins in low titer were demonstrated in about the same proportions in acute phase and in convalescent serum, and this streptococcus could therefore not be used for purposes of diagnosis.

In all the cases included in this study cold agglutinins, as mentioned before, were demonstrated in the serum. During the course of the illness, the earliest positive sample (fig. 1 A) was obtained between the 8th and the 28th day and the large majority were obtained during the second or third week. The last negative sample was obtained from the same cases during the first or second week. The highest titer (fig. 2), was found in most cases between the 10th and 28th day. In a few cases, however, the highest titer was registered as late as the 5th to 6th week, and in a few

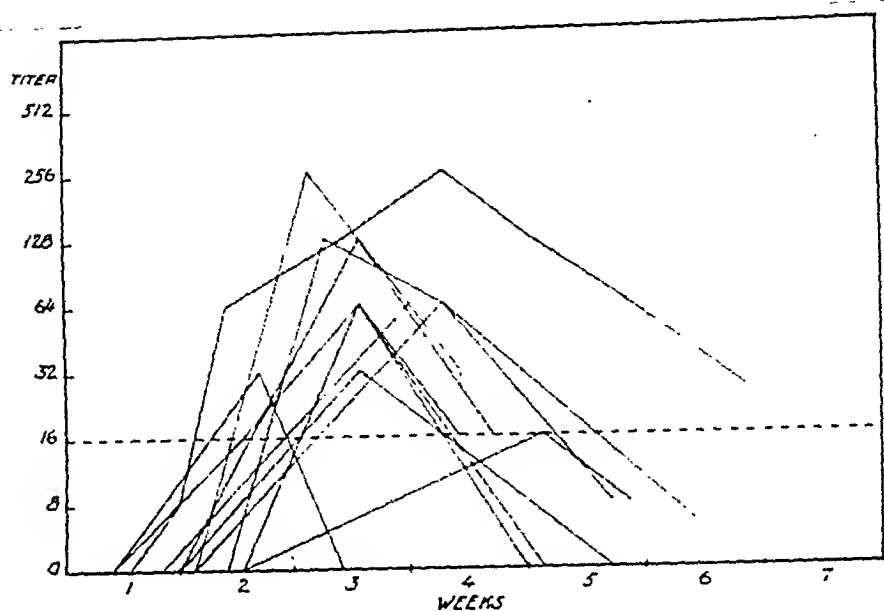


Fig. 3. Titers of cold agglutinins in a few representative cases.

cases between the 7th and 10th day. The first significant drop in the titer occurred between the 3rd and 5th week (fig. 1 B) and a titer of less than 1/16 was found in most cases after the 4th to 7th week (fig. 1 C). In a few isolated cases positive samples were obtained for as long a period as 2 months.

Figure 3 shows the course of the cold agglutination in a few representative cases. In those cases where the reaction never reaches high titers there is the risk that the point of time when a sure positive titer can be obtained will be missed if samples are not taken repeatedly at relatively short intervals.

Clinical Findings.

Epidemiology. The investigation included cases that occurred between May 21, 1945 and Oct. 1, 1946. The number of cases occurring in the different seasons of the year are shown in table 2.

During the first period, January to March 1945, only a few samples were sent in. More than 50 per cent of the cases occurred during October 1945 and between the months of January and March, 1946. This distribution of the cases indicates that the disease may be seasonal in type, with the majority of the cases concen-

Table 2.

Chronologic distribution of 112 cases of primary atypical pneumonia.

	Month	No. of cases within given range of months
1945	Jan. —March	5
	April—June	4
	July —Sept.	17
	Oct. —Dec.	37
1946	Jan. —March	24
	April—June	12
	July —Sept.	13

trated to the darkest months of the year as is the case in other acute respiratory tract infections. The disease attacked people of all ages and of both sexes. The majority of the patients, however, belonged to the lower age groups, below the age of 30 years.

The infectivity was not serious, and no particularly extensive epidemics occurred. On a couple of occasions, however, an epidemic spread was observable, both in a couple of families and among the children in a school. The latter epidemic has been described by Jonsson (16) from the Norrtull Children's Hospital. Another exception was that a number of nosocomial infections occurred; at Ersta Hospital, for instance, there was a small epidemic, with an Estonian refugee as the primary source of infection. The path of infection in this case was direct and intimate contact with the person affected, and there was in all probability no question of an air-borne infection.

Onset of the disease. In the present material, the onset was insidious in 53 per cent of the cases while in 47 per cent it was more acute. In those cases where the onset was insidious the commonest symptoms were weariness and general malaise. Coryza, cough, nausea and headache were also experienced by these patients. In cases where the onset was more acute the malaise was more pronounced and chills occurred in many cases. Pains in the muscles, generalized aches, and a sharp pain in the chest were also common symptoms. In many of these cases, it was impossible to distinguish the acute stage from influenza or pneumococcal pneumonia. As a rule, the general condition remained relatively unaffected in spite of the fact that the onset had been acute.

Symptoms during the course. The symptoms most commonly occurring during the patients' illness are shown in table 3.

Table 3.

Symptoms in 112 patients with primary atypical pneumonia.

Symptoms		Patients	
		Number	Per cent
General:	Headache	34	30
	Malaise	40	36
	Chills or chilliness	41	37
	Generalized aches	7	6
	Anorexia	10	9
	Nausea	4	3.8
	Vomiting	2	1.8
	Cough	101	90
Respiratory:	Sputum	40	36
	Bloody sputum	8	7.4
	Sore throat	9	8
	Chest pain	26	23
	Epistaxis	5	4.5
	Dyspnoea	7	6

Cough. Cough was the commonest symptom; in many cases it was the only noticeable one except fever. It was a hard, dry, irritative cough, which became looser, with mucoid or mucopurulent sputum, during the later part of the illness. The sputum was in some instances blood-streaked or blood-tinged. In many cases the amount of sputum was small during the entire course. The cough persisted, as a rule, during the febrile stage, in some cases long after the temperature had returned to normal, and was in many cases very troublesome.

Pains. Substernal pain, as well as pleural pain, was present in many cases. In a couple of patients these pains were focussed in the abdomen, and one patient was sent to the hospital on a diagnosis of acute abdominal disorder.

General condition. More than one-third of the patients experienced a certain degree of malaise, but on the whole the general condition, in all except the more serious cases, was unaffected.

Chills. Chills were experienced by about 40 per cent of the patients but in most instances they were mild. Fits of ague were rare.

Headache. Headache, which is stated in the American literature to be a very typical and common symptom, was only present in 30 per cent of my cases. As a rule it was mild and uncharacteristic.

Physical Signs.

The physical signs have been assembled in table 4.

Table 4.

Abnormal physical signs in 112 patients with primary atypical pneumonia.

Physical signs	Patients	
	Number	Per cent.
Fever	109	98
Nasal Congestion	11	10
Pharyngitis	71	63
Pulmonary signs	90	80
Dulness	42	37
Râles	82	73
Tachycardia	4	3.5
Cyanosis	9	8

Fever. Of the 83 patients whose temperature curve could be followed from the onset, 41 had a temperature of 39° C. or over during the first day. During the remainder of the course the fever was remittent; a continuous high fever or intermittent fever was uncommon. The drop in the temperature was generally lytic, a critical temperature drop being very rarely observed. The average number of days with fever was 12—15, varying between 4—6 days and up to 50 days.

Tachycardia and cyanosis were uncommon findings, and *herpes labialis* was only encountered in one patient.

Pharyngitis and rhinitis. Pharyngitis was present in 63 per cent and rhinitis in 10 per cent of the cases, usually in a mild form.

Lungs. The physical signs from the lungs were as a rule less pronounced than those found in lobar pneumonia. The most characteristic finding was diffuse râles, these occurring in 73 per cent of the patients. In only one-third of the cases was dulness established. The physical examination yielded a negative result in 20 per cent of the cases.

Course. The course of the disease showed considerable variation in the different cases. Only one death occurred. The other patients all recovered. The total time of illness, from the onset to the day when the patient was discharged, will be seen in figure 4.

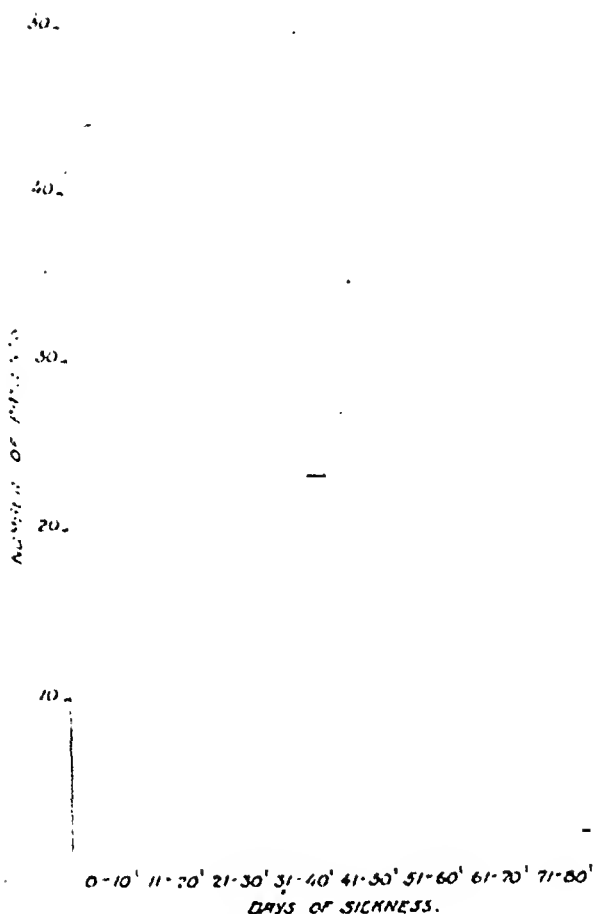


Fig. 4. Duration of sickness in 112 cases of Primary Atypical Pneumonia.

The majority of the patients were ill for 21—30 days and a relatively large number for 31—40 days. The disease in most cases took a much longer course than the course usually observed in lobar pneumonia.

Complications. Complications were rare. Acute sinusitis and otitis occurred in a couple of patients.

Chemotherapy, including penicillin. No very thorough attempt to judge the therapeutic value of sulfonamides and penicillin was made. Most of the patients were given sulfonamides in various dosages. Penicillin was, as a rule, given only at the hospital, and in these cases the treatment was carried out more consistently. No unequivocal results as regards the effectiveness of sulfonamides or penicillin were obtained.

X-ray Findings.

X-ray films of the lungs were taken in all cases, and in most instances they were also submitted to control examinations during the course of the illness. The X-ray showed, as a rule, more extensive changes than were indicated by the physical findings. A more detailed analysis will be furnished in a later publication. (36). Only a brief description of the commonest findings will therefore be given here. Usually, the pneumonic process was located in the lower lobes. In a little less than two-thirds of the cases the changes were present in one lobe only and in a little less than one-third in two lobes. In a few cases they were observed in 3, 4 or 5 lobes. Changes observable on the X-ray films were in most cases already present 1—2 days after the onset, and in a little over two-thirds of the cases they persisted for 3 weeks.

Two Typical Cases.

The most important results obtained from two cases¹ that could be followed in some detail have been assembled in figures 5 and 6, and a short description of the course of the illness will be given here.

Case 1. (Fig. 5.) A 45 year old business man became acutely ill, with malaise and a temperature of 40 degrees. Two days later he was admitted to the hospital. His general condition was then affected, he had

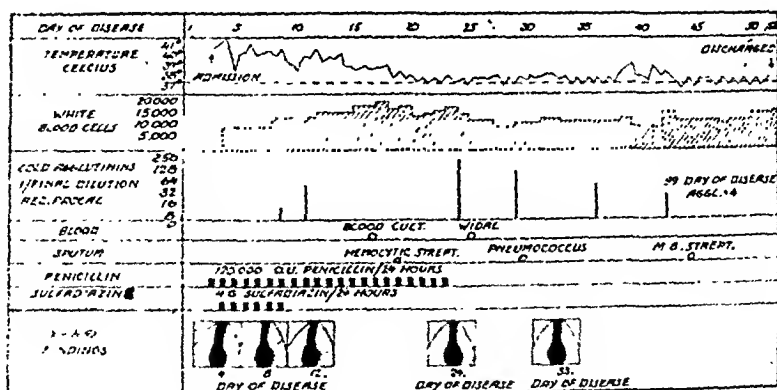


Fig. 5. Relevant findings and Therapy in a characteristic case of severe Primary Atypical Pneumonia.

¹ These two cases have kindly been placed at my disposal by Dr. A. R. Frisk.

high fever (41°C) and a severe cough with a little sputum. No cyanosis or dyspnoea. Râles were heard over the base of the right lung. He was treated with sulfapyrimidine and penicillin but without success. His temperature was around 39°C — 40°C for 12 days, and only after some time did it begin to fall gradually. During the first few weeks his general condition was strongly affected and he had auricular fibrillation for a time. The extent of the pneumonic process will be seen in figure 9. His cough became loose after a time with copious sputum. Cystopyelitis due to streptococcus faecalis, developed during the subsequent course. The diagnosis, primary atypical pneumonia, was confirmed by a positive cold agglutination test, which became positive about 8 days after the onset and reached its maximum at the end of the febrile period. The patient's general condition improved very slowly, and for a long time after his discharge he was convalescent; only after $2\frac{1}{2}$ months from the onset of the disease was he able to work at his full capacity.

Case 2. (Fig. 6.) A woman, aged 42, fell acutely ill with a temperature of 39.1°C , a dry cough, and a severe headache. Three days later sulfapyrimidine was administered but had to be withdrawn after one day because of severe vomiting. Five days after the onset the patient was admitted to the hospital. Her general condition was then relatively unaffected, but she complained of a severe headache and was troubled by a dry cough. The extent of the pneumonic process will be seen from figure 6. Penicillin therapy was tried but it had no effect. The tempera-

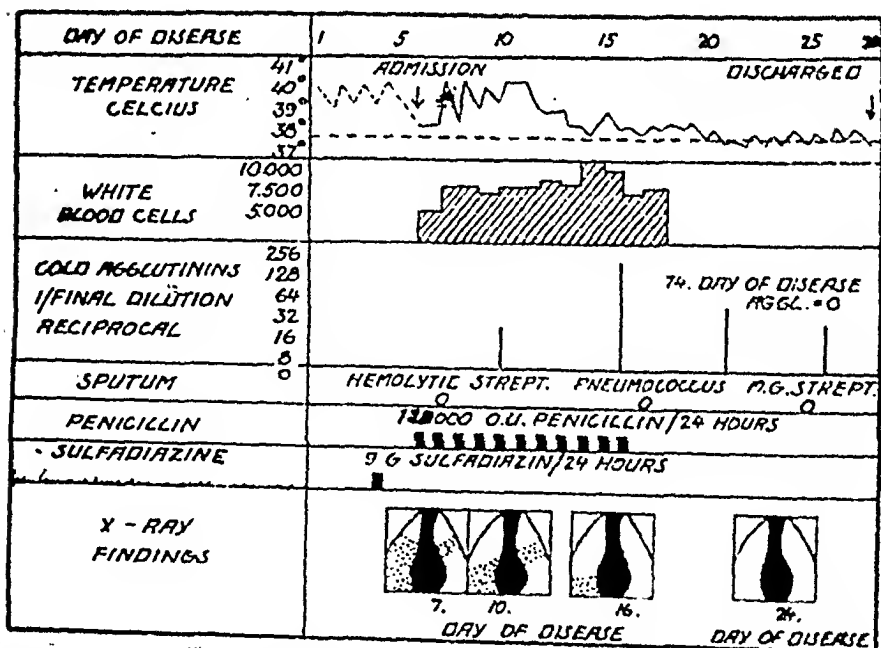


Fig. 6. Relevant findings and therapy in a characteristic case of Primary Atypical Pneumonia of Moderate Severity.

ture remained for another week around 38°—40° C and then began to show a lytic fall. The dry cough, which was one of the most troublesome symptoms, became looser in the later course of the illness. The diagnosis, primary atypical pneumonia, was confirmed by a positive cold agglutination test which in this case was demonstrated about 8 days after the onset and reached the highest titer at the close of the febrile period. After the temperature had returned to normal the patient rapidly improved, and about 3 weeks after the onset of the disease she was almost completely restored to health.

Factors Influencing the Cold Agglutination Titer.

In a number of American publications (5, 13) it is stated that the height of the cold agglutination titer is related to the severity of the disease, in other words, the higher the titer the more severe is the course of the disease, and vice versa. In order to ascertain whether similar conclusions could be reached with regard to my material, the highest cold agglutination titer obtained was compared with some of the symptoms that could be followed most closely. These were, first, the highest temperature lasting at least 24 hours that could be observed; second, the number of days the fever lasted; and third, the highest number of white cells occurring during the course of the disease. The results have been assembled in table 5.

Table 5.

Relation of maximum cold agglutinin titer in 97 cases to the height and duration of fever and to the leukocyte count.

Maximum titer	> 16	16—32	64—128	256—512	Total
Maximum temperature					
Less than 38° C		1		1	2
38°—39°		4	2	2	8
39°—40°	1	15	29	12	57
40° or higher		4	15	11	31
Totals	1	24	46	26	97
Duration of fever					
7 days or less	1	7	2		10
8—14 days		11	22	3	36
15—21 days		5	15	17	37
22 days or more		1	7	6	14
Totals	1	24	46	26	97
Leukocyte count					
Less than 7,500	1	12	12	5	30
7,500—12,500		7	25	13	45
12,600 or more		5	9	8	22
Totals	1	24	46	26	97

It will be seen from the table that the height of the fever is not in direct relation to the cold agglutination titer. The distribution around the commonest titer of 1/128 is fairly even. Looking at the duration of the fever, we find a better correlation. The cases fall into fairly distinct groups, with the majority of those where the duration of the fever was short grouped around the lower titer levels and those with a greater number of days with fever around the higher titers. The same features are apparent on a comparison with the highest leukocyte count during the course of the disease.

Discussion.

The investigation has shown that the cases of primary atypical pneumonia that have occurred in Sweden show in all essentials the same features as those described by Anglo-American investigators.

Contrary to the observations made by American investigators, however, even cold agglutination as low as 1/16 had diagnostic value in my series, as has been mentioned before.

The preliminary experiments carried out with a view to demonstrating a specific virus have hitherto been negative.

Of the other clinical laboratory findings the white cell count and the sedimentation rate were attributed diagnostic significance. Contrary to the findings in bacterial pneumonia, the white cell count has been stated to be normal or only moderately raised in this disease. This was found to be the case in the present series also, although the more severe cases often had leukocytosis. The sedimentation rate has been said to be low or only moderately raised. In the present series, high sedimentation rates were common, and this reaction is therefore of no great significance for the differential diagnosis.

The clinical picture showed considerable variation and no uniform and dominating disease type could be distinguished. The gradual onset, with fever, cough, and headache, mentioned by American authors as characteristic, was not the dominating characteristic in my series; an acute, non-specific onset was just as common. The symptoms during the remainder of the course, and the abnormal physical signs, were on the whole the same as those described in American publications, however. A few small differences were observed, however. The initial fever, for instance, was in most cases higher than has been stated as common, and the

typical headache was only present in some of the severest cases, while in the milder cases it was very uncharacteristic.

Treatment with sulfonamide compounds and penicillin does not seem to have had a noticeable effect on the course of the disease.

Summary.

A clinical and etiological study of 112 cases of primary atypical pneumonia occurring during the time of Jan. 1945—Sept. 1946 in Sweden is reported. Only cases with a positive cold agglutination test are included in the material. The significance of the cold agglutination test compared with some of the laboratory findings and clinical symptoms is discussed.

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Neue Ergebnisse über die Ethnologie der bösartigen Geschwülste.

Von

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(Bei der Redaktion am 6. Mai 1947 eingegangen.)

In meinem Aufsatz »von der Virus-Entstehung der Geschwülste« (Acta med. Scand. V. 125 Fasc. II) hob ich hervor, dass alle bisher angegebenen Theorien der Genesis der Geschwülste in zwei diametral entgegengesetzte Richtungen zerfallen: 1) die Transformationstheorie und 2) die Theorie der parasitären Herkunft der Geschwülstzelle selbst.

Ungeachtet dessen, dass die Transformationstheorie 4000 Jahre in der Medizin existiert, hat keiner, ihre Richtigkeit bewiesen, und ich erlaube mir ihren pseudowissenschaftlichen Charakter hervorzuheben, infolge dessen, dass die Erklärung der Genesis der Geschwülste nicht auf experimentellen Ergebnissen, sondern auf rein spekulativen Schlussfolgerungen beruht, was für die Wissenschaft nicht annehmbar ist.

Wenn zu den Hindu-Zeiten, Hippocrates, Galen's, der Kartesianischen Schule und sogar im Jahre 1842—43, als Andral und Vogel, die Theorie der Herkunft der Geschwülste aus Blasteme vorlegten — sogar damals erschien die Transformationstheorie als reinste Phantasie, die nachfolgernd die Primitivität des wissenschaftlichen Denkens der alten Medizin fortsetzte.

Erst im Jahre 1801 machte Bichat den Versuch die Transformationstheorien wissenschaftlich zu begründen, indem er als Grundlage seine Forschungen über die Gewebe des Organismus legte: er bot die Theorie der Bildung der Geschwülste aus dem Bindegewebe an.

Indem Cruveilhier diese Ansichten weiter vorrückte gab er zum erstenmal im Jahre 1814 die Idee der kankrösen Degeneration der Gewebe, die im Grunde der Krebsbildung liegt, was auch reineste spekulative Vermutung war.

Aber die Ideen von Bichat und Cruveilhier benutzte im Jahre 1858 Virchow für seine Theorie, indem er behauptete, dass die jungen, indifferenten Zellen der Bindegewebe sich unter dem Einfluss des chronischen Reizes in Zellen einer beliebigen Geschwulst, verwandeln. Den Mechanismus der Wirkung des chronischen Reizes verglich Virchow mit der Befruchtung der Eizelle durch den Spermatozoid.

Das war auch eine reine spekulative Theorie, deren vitalistischer Charakter der Erklärung des Mechanismus der Malignisation der Organismuszellen, die diese Theorie annimmt, ihre völlige Unwissenschaftlichkeit zeigte.

Virchow gründete sich auf oberflächliche Beobachtungen der klinischen und patholog-anatomischen Ergebnisse, die die Geschwülste begleiten und hielt diese sekundären Unterstützungsmomente für ethiologische.

Die grosse Autorität des Begründers der Zellulärpathologie zwang diese Theorie als Axiom anzunehmen, dass die Zellen der Geschwulst, aus den Zellen des Organismus entstanden sind, obwohl kein Beweis dessen, weder damals, noch bisher angeführt worden ist.

Die unendlichen Experimente zeigten, dass ein chronischer Reiz, der im Lauf von einem Drittel des Lebens eines Tieres ausgeführt worden ist, nicht immer zu einer Entwicklung der Geschwulst führte. Eine Zeitlang schien es, dass die hervorragenden Versuche von Jamagiwa und Itshikawa eine Bestätigung von Virchow's Theorie boten, aber jetzt ist es bewiesen, dass der chronische Reiz nicht als ethiologische Ursache der Geschwülste angesehen werden darf, er bildet nur die Anlage des Organismus dazu (G. Schor).

Ebenso wird auch eine Anlage des Organismus durch kanzerogene Stoffe hervorgerufen, die nur den % der spontanen Geschwülste steigern. Es ist bekannt, dass Geschwülste, die durch Kanzerogene hervorgerufen worden sind, durch zellenlose Filtrate verimpft werden können (Mack-Intosh, Selbie, Pentimalli, Parsons, Judina und Tschernjaewa und and.) — was ihre Virus-Genesis beweist. Indem die Kanzerogene die antiblastischen Kräfte des Organismus hemmen und die Tätigkeit der Viruse aktivisieren, rufen sie

nur eine Erhöhung des % der spontanen Geschwülste hervor, was die verschiedene histologischen Bauart der durch ein und denselben Kanzerogen hervorgerufenen Geschwülste, beweist.

Auf diese Weise ist die Fähigkeit, durch chronischen Reiz Geschwülste hervorzurufen, die Virchow's Theorie annimmt, jetzt widerlegt. Widerlegt ist auch die Grundlage dieser Theorie, von der Herkunft aller Geschwülste von den Bindegeweben. Im Jahre 1837 hat Gluge als erster auf die Herkunft des Hautkrebses von dem Epithel der Hautdrüsen gewiesen. Im Jahre 1852 hat Remack deutlich auf die epitheliale Genesis des Krebses gewiesen, worin er von Lebert, Cornil u. a. unterstützt worden ist.

Von den russischen Autoren vor Thirsch und Waldeyer ist die epitheliale Genesis des Krebses von M. Scharbe 1861 und Stradomski 1863 beschreiben worden. Unwiderrufen blieb nur die Grundlage von Virchow's Theorie von der Herkunft der Geschwülstzellen von den Zellen des Organismus.

Aber eine ganze Reihe misslingener Versuche diese Grundlage zu beweisen, zwang noch im Jahre 1878 Professor W. Paschutin zu schreiben, dass »alle Versuche der Koryphäen der Wissenschaft, die Herkunft der Geschwulstzellen von den Zellen des Organismus zu beweisen, zu keinem Resultat führen, aber der Mechanismus der Bildung der Krebszellen, der von der Theorie von Cohnheim angenommen worden war, ist experimentell widerlegt«. Im Jahre 1909 schrieb Akademiker Ssubbotin dass »die Natur der Geschwulstzelle bis jetzt nicht aufgeklärt ist«.

Von den russischen Cythologen schrieb A. W. Rumjanzew 1932, dass es bis jetzt nicht aufgeklärt ist, aus welchen Zellen die Geschwulst bestehe. Im Jahre 1940 wies N. G. Chlopın, indem er 4 Arten der Zellen der R-Sarcome beschrieb, darauf hin, dass die Gewebenatur dieser Elemente im Dunkeln bleibt, aber aus dieser Beschreibung klärt sich ganz deutlich die Anwesenheit der cyclischen Veränderungen der Zellen der R-Sarcome auf.

Auf diese Weise bleibt das allgemein angenommene Dogma von der »Zellennatur« der Geschwulstzelle bisher nicht bewiesen und die nächsten Untersuchungen der Histogenese der Geschwülste, widerspricht vollkommen diese Konzeption.

Wie bekannt, begnügt sich die Medizin bisjetzt mit der spekulativen Vermutung von Hoeber, dass »die Krebszelle ein biologisch verändertes Epithel ist« (1875), doch bisher sind keine Beweise dafür angeführt worden.

Die vielfachen Versuche den Mechanismus der Verwandlung

der Epithelien in Krebszellen aufzuklären, führte sehr oft zu vitalistischen Auffassungen desselben. Waldeyer schrieb z. B. 1867 von der plötzlichen Verwilderung der Epithelien, ihren Verlust des Altruismus und des Erwerbens des Egoismus; Burchgart — vom revolutionären Charakter der Epithelien; Petroff — von der räuberischen Lebensweise des Epithels, das einen inneren Streit im Organismus hervorruft. Leider wurden diese wilden Vorstellungen von dem biologischen Prozess, der in dem Geschwulstorganismus verläuft, für wissenschaftliche medizinische Theorien der Genesis der Geschwülste herausgegeben und hemmten unstreitig das wissenschaftliche Fortschreiten der Onkologie, indem sie die Tatsachen der Verusche mit Fachausdrücken, Phantasien und spekulativen Anschauungen untertäuschten, die der echten Wissenschaft fremd sind.

Deshalb ist das Problem der Genesis der Geschwülste bis jetzt nicht gelöst und wird durch die pseudowissenschaftlichen Transformationstheorien verdeckt.

Aber es ist nicht ohne Interesse daran zu erinnern, dass noch im Jahre 1861 der russische Professor E. Pelikan eine begeisterte Kritik von Virchow's Theorie gab. »Die Schatten der Archeies und der Pneumae kommen in dem bildenden Reize in den Zellen zum Vorschein. Man muss Kenntnisse der molekulären Verhältnisse haben, aber das mechanische Übertragen der pathologo-anatomischen Bilder in die Sprache der katalytischen Prozesse, kann nichts geben.»

Deshalb bedurfte man der vielfachen Verbesserungen von Virchow's Theorie, um den Versuch zu machen, eine wissenschaftlich begründete Erklärung der Genesis der Geschwulstzelle zu geben. Aber beim fortschreitenden Prozess des Erlernens der Genesis der Geschwülste sind die ungenügenden Verbesserungen von Ribbert, Hansemann, Borst u. a. abgefallen.

Die Reihe, ist auch an die Theorie von Fischer-Wasels gekommen, die noch 1914 von Prof. Sükow gegeben wurde und die auf die Basis der im Jahre 1891 von E. Basilewitsch gestellten Voraussetzung beruht, dass im Grunde der Krebsentwicklung die Störung des Regenerationsprozesses liegt.

Die Theorie von Basilewitsch-Sükow-Fischer-Wasels nimmt, als Grundlage des blastomatösen Wuchses die Geschwulstkeimanlage, auf die noch Virchow gewiesen hat, aber dessen tatsächliche Existenz bisher niemand bewiesen hat. Dieser »Keim« entwickelt sich infolge der embryonalen Anomalien oder leichter Störungen

des Regenerationsprozesses — was eine vollkommene spekulative Vermutung ist, aber keine Facta. Die Anwesenheit von Mutation die »den Keim« in eine Krebsgeschwulst verwandelt, ist auch ein ausgedachter Leitsatz. Durch Mutation hat noch niemand eine Zelle des Organismus in eine Geschwulstzelle verwandelt. Die klare wissenschaftliche Unvollkommenheit der Theorie von Basilewitsch-Siikow-Fischer-Wasels besteht in dem Mangel der experimentellen Bestätigung ihrer Leitsätze, die die Forderungen von Boyle der experimentellen Begründung jedes angenommenen Satzes der gebotenen Theorie, ignoriert.

Die letzten Arbeiten der russischen Cythologen (Chlopin, Garschin u. a.) zeigten, dass die Embryogenese nicht wiederholbar ist und dass die histophysiologische Determination der Zellen, die in der Embryogenese erhalten wird, unveränderlich ist. Die Zelle kann in keinem Falle ihre biologischen Eigenschaften verändern und sich in eine andere Gattung von Zellen verwandeln. Die Metaplasie der Zellen ist nur im Gebiet derselben Art der Zellen möglich. Das Epithel der Gedärme kann sich nicht in ein Epithel der Hautdecke verwandeln oder in die Mesenchymzellen und umgekehrt. Die Geschwulstzelle bildet keine Gewebe und besitzt keine Eigenschaften derselben (Chlopin).

Daraus wird klar, dass die Theorie von Hoeber von den sich verändernden biologischen Eigenschaften des Epithels, dass sich in eine Krebszelle verwandelt hat, absolut falsch ist, da das Epithel unter dem Einfluss des Prozesses der allmählichen Malignisation, sich nicht in eine Krebszelle verwandeln kann. Auf diese Weise ist die Lehre von Orth vom Vorkrebs völlig unbegründet und falsch. Also ist es klar, dass die Zellen der Geschwulst nicht von den Zellen des Organismus abstammen, da sie ganz andere biologische Eigenschaften besitzen. Auf diese Weise ist es aufgeklärt, dass Virchow's Theorie die fast 100 Jahre den biologischen Begriff des Problems der Onkologie hemmte, wissenschaftlich ungenügend ist.

Völlig widerrufen ist auch die Theorie von Cohnheim, denn bisher ist es keinem gelungen im Experiment aus embryonalen Zellen Geschwulstzellen zu erhalten, was noch im Jahre 1910 von M. Thiesenhausen vielseitig gezeigt wurde.

Die Hinweisungen von Askanasi, Petroff u. a. dass es ihnen gelungen sei, den Krebs und die Sarcoma durch Zusatz kleiner Dosen von As zu den embryonalen Zellen zu erhalten, sind falsch — sie hatten in ihren Versuchen nur ein seltenes Erscheinen in

den späten Etappen des Experiments (bei Petroff im 18–27 Monat) der spontanen Geschwülste.

Auf diese Weise ist die wissenschaftlich ungenügende Begründung der Theorien von Virchow, Cohnheim, Fischer-Wasels jetzt aufgeklärt und ihr spekulativer Charakter aufgedeckt. Aber bis jetzt lassen die für die deutsche Onkologie charakteristischen Versuche, das Problem des blastomatösen Wuchses mit Hilfe von spekulativen Schlussfolgerungen zu lösen, nicht nach.

So hat Petroff im Jahre 1941, indem er die Resultate der Forschungen von Chlopin, Garschin u. a. im Auge hatte, erkannt, dass der chronische Reiz die Zellen des Organismus nicht malignisieren kann, denn ihre biologische Determination störte dabei, aber um die Reste der Theorie von Virchow von der »Zellennatur« der Geschwulstzelle zu retten, liess er spekulativ die Möglichkeit der Existenz verschiedenartiger »Mutagene« zu, die eine plötzliche Mutation der Zellen und auf diesem Weise eine Veränderung ihrer histophysiologischen Eigenschaften hervorrufen. Aber die Tatsache der Anwesenheit der somatischen Mutation in den Zellen der Tiere ist mit Bestimmtheit nicht bewiesen, desto mehr der Mutationscharakter der Malignisation der Zellen.

Aus den Arbeiten des Genetikers Herschensohn (1937) ergibt es sich mit Deutlichkeit, dass man gar keinen Grund hat von der Mutationsgenese der Geschwulstzelle zu sprechen, welche Behauptung dem wissenschaftlichen Begriff der Mutation widerspricht.

Auf diese Weise spielt jetzt die Benennung »somatische Mutation« die Rolle »deus ex machina« der römischen Tragödien. Ausserdem enthüllen die Fakta der Übertragung der Geschwülste durch die zellenlosen Filtrate, wo keine Zellen und folglich keine Möglichkeiten für das Verlaufen der Mutation sind, mit aller Deutlichkeit die Unrichtigkeit dieser Zulassung.

Wenn wir dazu hinzufügen, dass es bisher keinem gelungen ist weder mit Kanzerogenen, noch Viren in der Gewebe-Kultur der Organismuszellen zu malignisieren, und auch in vivo malignisiert die Geschwulst nicht die mit ihr benachbarten Zellen, so tritt mit voller Deutlichkeit die Unbeweisbarkeit des Dogmas der Herkunft der Geschwulstzellen von den Zellen des an der Geschwulst erkrankten Tieres.

Auf diese Weise wurde durch die Fakta, die die Wissenschaft erhalten hatte der pseudowissenschaftliche Charakter der Transformationstheorie, an den Tag gelegt und es ist durchaus not-

wendig, sich ernsthaft in die tatsächliche Begründung der Theorie der parasitären Genesis der Geschwulstzelle selbst, hineinzudenken.

Adams wies als erster im Jahre 1796 auf die parasitäre Natur der Geschwülste, indem er sie zu einer eigentümlichen Art von Würmern rechnete. Eine ähnliche Meinung drückte auch 1836 Carmichael aus, indem er die Geschwülste zu einer Art von tierischen Schwämmen rechnete. .

Der erste, der die den Organismuszellen fremde Natur der Geschwulstzelle verurteilte, war J. Müller 1838, indem er hinwies dass sie von dem »Seminium morbi« stammt. Hannover 1843 gründete die Lehre von der »cellula canerosa specifica«, das wurde von einer Reihe französischer Gelehrten — Lebert, Seidillot, Robin, Führer u. a. unterstützt. Aber ein Gegner dieser Theorie war Virchow vom Jahre 1848 und sie wurde von den Autoritäten nicht anerkannt. 1881 sprach Odenius deutlich von der parasitären Herkunft der Geschwulstzellen und 1893—1903 erweiterte und begründete diese Theorie Adamkiewitz, indem er auf die Eigenart der Vermehrung und des Baues der Geschwülste wies, die sich stark von den Schichten der Epithelien unterschieden — aber die Onkologie schenkte diesen Arbeiten wenig Aufmerksamkeit.

Ungeachtet der völligen Impopularität dieser Theorie, begann ich auf Grund des vieljährigen Studiums der Cythologie der sich entwickelten Geschwülste von Stamm Flexner-Jobling 1930, zu behaupten, dass die Stammgeschwülste parasitärer Natur seien, indem ich zyklische Veränderungen der Krebszelle fand, was mir unstreitig als ein Beweis ihrer parasitären, den Organismuszellen fremden Natur schien. Die riesigen Schwierigkeiten der Bestimmung des Zyklus der Krebszellen und die sich nicht selten beimischende Invasion mit anderen Parasiten, bedingten die vorläufige Einreihung von mir, des Krebsparasiten zu der Klasse der Sporozoa, während er der Klasse der Chlamydozoa am ähnlichsten ist.

Indem ich im Jahre 1933 die Anwesenheit filtrierender Stadien im Zyklus der Entwicklung der Krebszelle konstatierte, ergänzte ich meine Theorie durch die vorläufige Einreihung der Geschwulstzelle zu den eigenartigen Parasiten, die ultramikroskopische Stadien in Zyklus ihrer Entwicklung besitzen (1934).

Da die Natur der Viruse von der Wissenschaft noch nicht genau aufgeklärt ist, aber einige Protozoa, nach Schaudin unzweifelhaft in ihrem Zyklus filtrierende Stadien haben, so scheint es mir, dass

die Frage über die Natur des Geschwulsterregers weiterhin einer experimentelle Untersuchung zur genaueren Bestimmung ihrer Herkunft bedarf.

Die Filtrierbarkeit der Geschwülste lässt in Wirklichkeit vor Allem die Frage von ihrer Virusnatur beantworten, was von mir in dem obenerwähnten Aufsatz gemacht worden ist, wo Fakta angeführt worden sind, die die Virus Genesis der Geschwülste zulassen und auch ausschliessen.

Aber die Tatsache selbst der Filtrierbarkeit des Krebses der Säugetiere ist bis zur letzten Zeit nicht bewiesen, woher ich Ergebnisse über meine vieljährigen Versuche der Filtrierbarkeit der Geschwülste, anführte. Die Versuche die vom Jahre 1933 in meinem Laboratorium ausgeführt worden waren, zeigten, dass von 347 Experimenten der Ultrafiltrierung »in vivo« der verschiedenen Stämme (Flexner-Jobling, Jensen, Kritschewsky-Sinoelnikow, Ehrlich, Rous u. a.) 185 Geschwülste erhalten wurden. Im Prozess der Prüfung der Methode nähten wir nicht nur Kollodiumsäcke in die Bauchhöhle ein, indem wir ihren Stumpf (Verklebungsplatz) unter die Haut einführten, sondern überzeugten uns auch durch Filtrierung verschiedener Farben, dass der Stumpf nur die Farben durchlässt, die die Membrane durchgehen. So kann man mit Kollargol — dessen Molekül $20\text{ m}\mu$ beträgt — das Säckchen füllen und es dem Tiere einnähen, damit es im Laufe von mehreren Monaten ohne Veränderungen bleibt und auch nicht aus dem Säckchen durch den Stumpf in vitro filtriert wird. Das 3-monatliche Befinden des Säckchens in der Bauchhöhle der Ratten, veränderte nicht die Grösse seiner Poren.

Indem wir streng kalibrierte Membranen (nach Teague-Buxton) von $15\text{--}20\text{ m}\mu$ hatten, konnten wir kein Durchgehen sogar der Zwergzellen von Borst, die die Grösse von $0.1\text{--}0.2\text{ m}\mu$ haben, erhalten. Es wurde 8—10 % Kollodium genommen. Als Petroff meine Versuche wiederholte, erhielt er 20 filtrierbare Geschwülste, aber da er die Geschwulst in 2 Säckchen einnähte, konnte er natürlich keine Entwicklung der Geschwülste erzeugen. Er schrieb, »warum könnte der lebendige Virus nicht zwei Membranen passieren«.

Die Naivität und Unbegründung dieses Einwandes ist offenbar; es ist verständlich, dass nur der Virus der zweimal so klein ist als der Virus der Geschwülste, durch 2 Membranen durchdringen konnte und nur dann, wenn die Virizidstoffe des Blutserums ihn noch nicht zerstört hatten. Die Ultrafiltrierbarkeit der Geschwülste

ist längst bewiesen; noch im Jahre 1931 hatten Mendelsohn, Clifton, Lewis, Fränkel sie ganz genau für die R. Sarcome gezeigt, was die »Zellennatur« der Geschwülstzellen ausschliesst, da die Zellen der Tiere durch die Kollodiummembranen nicht durchgehen können und keine ultramikroskopischen Stadien haben. Aber auch die Viruse können nicht die Organismuszelle in eine Geschwülstzelle verwandeln, da sie ihre histophysiologische Determination nicht verändern können.

Da die Ultrafiltrierbarkeit der Virusgeschwülste bewiesen ist, hat der Einwand von Petroff keine wissenschaftliche Bedeutung.

Die Ultrafiltrierbarkeit der Geschwülste ist bewiesen.

R-Sarcome	1931	Mendelsohn Clifton Lewis Fränkel
Krebs der Ratten und Mäuse; Sarcome der Ratten	1933	Newiadomski
Sarcome der Mäuse	1934	Besredka u. Gross
R. Sarcoma	1934	Irvin, Basting, Gairns
R. Sarcome	1935	Claude
Krebs der Mäuse und Ratten, Sarcome der Hühner und Ratten	1935	Runowa
Krebs d. Mäuse und Ratten	1936	Petroff und Krotkina
Lymphogranuloma	1935	Miygawa
Fibrome des Kaninchen	1937	Andrewes und Schlesinger
Papillome des Kaninchen	1937	Andrewes und Schlesinger

Wie bekannt, lässt Petroff die zellenlose Übertragung der Geschwülste nicht zu, obwohl er selbst 20 ultrafiltrierbare Geschwülste erhalten hat.

Daher sind die von mir angeführten Fakta des Erhaltens von 185 ultrafiltrierbaren Geschwülsten verschiedener Stämme der Ratten und Mäuse, von grosser prinzipieller Bedeutung, da sie die ultramikroskopischen Dimensionen des Geschwulsterregers beweisen.

Es ist bekannt, dass kein einziger Krankheitserreger die biologische Determination der Zelle verändern kann und ihr neue biologische Eigenschaften geben kann. Es ist wahr, dass die Viruse in der Kultur die Zellengewebe nicht malignisieren, keine Mutation hervorrufen und nur zu gewöhnlichen degenerativen Veränderungen führen. Daraus erfolgt, dass Viruse im Unterhaut-

zellengewebe keine epithelialen Zellen aus mesenchimalen Zellen bilden und Zellen des Ehrlich's Stammes nicht bilden können, deren Entwicklung ich bei meinen Versuchen beim Einnähen unter die Haut von Kollodiumsäckchen mit Ehrlichsstamm (wie auch mit Flexner-Joblingsstamm) erhielt.

In Organismus der Mäuse gibt es keine Zellen des Ehrlich's Stammes wie auch keine Zellen anderer Stämme. Woher entwickeln sie sich denn beim Einführen von zellenlosen Filtraten, die nur dieselbe Bauart von Geschwülsten erzeugen, die für die Vorbereitung des Filtrats genommen wurde? Sogar der Stamm Fujinami, der von Filtrat R-Sarcome bekommen worden ist, zeigt eine Entwicklung derselben an den Enten; der Stamm Fujinami ist nicht aus den Zellen der Ente gebaut; er entwickelt sich als Hühnergeschwulst, als R-Sarcome.

In den Versuchen an Ratten von Putnoky und de Balogh entwickelte sich eine Mäusegeschwulst aus den eingeführten Zellen der Mäusegeschwulst, aber nicht aus den Zellen des Organismus der Ratten. Diese Versuche weisen deutlich auf die Unmöglichkeit der Malignisation der Zellen des Wirts — die Geschwulst entwickelt sich immer »aus sich«, indem sie die benachbarten Zellen des Organismus der Tiere nicht ansteckt und sie nicht malignisiert. Weder in vitro in der Kultur der Gewebe, noch in vivo — um die Geschwulst herum, geschieht eine Malignisation der Organismuszellen.

Daraus geht unumgänglich die Folgerung hervor — dass die Zellen der Geschwulst aus den elementaren Körperchen sich entwickeln, die in dem zellenlosen Filtrate zu haben sind. Die Grösse dieser Körperchen ist in den Filtraten verschiedener Geschwülste verschieden. Im Jahre 1939 sind von mir elementare Körperchen in allen Stammgeschwülsten, die in meinem Laboratorium waren, konstatiert.

Jetzt teilen eine Reihe von Autoren von dem Wuchs der elementaren Körperchen in den Kulturen mit (Paschen, Malamos u. a.). Mit Hilfe der Kultur der elementaren Körperchen erhielt Rooyen die Myxome der Kaninchen und Mijagawa die Lymphogranulome.

Diese Fakta zwingen uns die elementaren Körperchen als ultramikroskopischer Erreger streng bestimmter Geschwülste anzusehen, denn jetzt ist die Anwesenheit von spezifischen, gegen die elementaren Körperchen der Antikörper im Blute der an Geschwülsten leidenden Tiere bewiesen und auch der Viruszer-

störenden Stoffe. Diese Fakta genügen vollkommen, um die ultramikroskopischen Dimensionen des Geschwulsterregers als bewiesen anzunehmen, aber die Genesis der Geschwulstzelle muss sich einem weiteren experimentellen Studium unterwerfen.

Noch im Jahre 1930 wurden von mir zyklische Veränderungen der Geschwulstzelle bemerkt, die die Stadien Elementarkörperchen, Initialzelle, Schizonten, durchmachten. Letztere sind in meinen Arbeiten im Jahre 1934 (*Le Cancer*, vol. XI) beschrieben worden. Diese Ergebnisse sind von mir beim Erlernen der Histogenese der Geschwülste, die sich um die Kollodiumsäckechen entwickelten, bestätigt worden.

Es war nicht schwer sich davon zu überzeugen, dass, wenn man täglich (im Laufe von 24 Tagen) die Histogenese dieser Geschwülste verfolgte, in den ersten 3—4 Tagen des Versuches eine Ansammlung von Initialzellen in der Nähe der Kollodiummembrane geschieht. In den folgenden Tagen bemerkte man eine Vergrößerung der Dimensionen der Initialzelle und ein Erscheinen der Schizonten oder der Zwergkrebszellen. Vom 5-ten Tage an sahen wir lymphocytenähnliche kleine Krebszellen; die sich später in einer reifen Form verwandelten. Von mir sind die Formen der zyklischen Veränderungen des Kernes der Schizonten und die Anwesenheit in ihm der Bilder der Karyokinese (*Le Cancer*, vol. XI 1934) beschrieben worden.

Eine ähnliche Veränderung der Schizonten oder der Zwergkrebszellen ist in den Arbeiten von Mauer 1938 angeführt, wo die Anwesenheit im Exudate des Ehrlich's Stammes der Zwergzellen beschrieben ist. Im Jahre 1936 wurden sie von Borst und vor ihm von Thoma 1889, von I. Koch und von mir unter dem Namen Schizonten beschrieben. Auler, Hohenadel und Maner konstatieren die Evolution des Kernes der Zwergzellen und die Anwesenheit in ihm der Karyokinese, die noch im Jahre 1934 von mir erwähnt wurde. Wenn man diese Ergebnisse mit der obenerwähnten Arbeit von Chlopin von den Zellen der R-Sarcome vergleicht, muss man hervorheben, dass die zyklischen Veränderungen der Geschwulstzelle ihre parasitäre Natur beweisen, was noch im Jahre 1927 aus den Arbeiten von Haagen hervorging. Er bestätigte die Möglichkeit der Überimpfung der R-Sarkome durch getrocknetes Pulver der Geschwulst und aus ihm die Zelle R-Sarcome zu explantieren. Diese rufen beim Einimpfen den Hühnern eine Entwicklung der Geschwulst hervor. Diese Fakta bewiesen mit voller Überzeugung den parasitären Ursprung der Zellen der R-Sarkoma, da die Zellen

des Huhnes ihre Lebensfähigkeit im Laufe von einigen (8) Monaten, indem sie sich im getrockneten Pulver befanden, nicht bewahren konnten.

Unwiderruflich hat die Geschwulst morphologisch einen histoiden aber keinen organoiden Charakter, da sie keinen diploblastischen Charakter des Aufbaues besitzt, was noch im Jahre 1919 Korsehun, Prjewalski und Trinkler behaupteten. Diese Autoren zeigten, dass die Lage der Geschwulstzellen den Protozoen Kolonien ähnlich ist und dass die Behauptung von der parasitären Natur der Krebszelle streng wissenschaftlich ist.

In der Kultur der Gewebe unterscheidet sich wesentlich nach den Ergebnissen von Chlopin, meines Laboratoriums und vieler anderer Zytologen, das Wachstum der Geschwulstzellen vom Wachstum der Organismuszellen.

Es ist interessant zu erfahren, dass im Jahre 1944 Morosenskaja den Stamm der Hepatome der Maus, den sie durch Kanzerogene bekommen hatte, beschrieb; bei seiner Entwicklung unter der Haut bleibt seine morphologische Ähnlichkeit mit der der Leberzellen erhalten, aber sie produzieren weder Galle noch Glykogen. Dieses Faktum dient als klare Widerlegung der Ansicht von der Bewahrung der Geschwulstzellen der Fähigkeit, spezifische Stoffe der Drüsen des menschlichen Organismus, abzusondern.

Auf diese Weise erscheinen die obenerwähnten Fakta des Experiments als solide wissenschaftliche Begründung der von mir im Jahre 1934 gebotenen Theorie von der Herkunft der Zellen der bösartigen Geschwülste von Elementarkörperchen, aber für das endgültige Anerkennen dieser Theorie ist es notwendig in der Kultur die Verwandlung der Elementarkörperchen in Geschwulstzellen zu erhalten, was auch der Gegenstand unserer Forschungen ist. Augenblicklich haben wir die Ansammlung vom Elementarkörperchen des Flexner-Joblings Stamms in der Kultur erhalten.

Conclusions.

1) The fundamental error of method in oncological research is based on the application of the transformism theory, which admits idealistic and vitalistic conceptions for the interpretation of the genesis of tumors. This interpretation is founded not on experimental findings or observation, but on speculative data, a fact which clearly demonstrates the pseudoscientific character of the

transformism theory beginning from Virchow and up to Fisher-Vasels.

2) Recent investigations of cytologists demonstrating the impossibility of changes in the histophysiological properties of body cells, determined in embryogenesis, clearly reveal the non scientific basis of the theory of malignisation of cells by chronic irritation and of the occurrence of precancerous states.

3) The fact that absolutely specific tumors can be obtained by means of cellfree tumor filtrates obviously proves that the mutation theory (transformation of normal cells into neoplastic ones) lacks sound scientific basis.

4) Viruses are unable to alter the histophysiological properties of cells and to bring about mutation; therefore it becomes necessary to investigate the possibility of formation of a malignant tumor from elementary bodies present in the cellfree tumor filtrate.

5) As a matter of fact, absolutely specific tumors can be obtained from cellfree tumor filtrates; this suggests that the true agents of tumors are elementary bodies.

6) On the basis of the above mentioned data, the hypothesis suggesting that tumor cells derive from elementary bodies — the true agents of tumors — can be considered as fully justified.

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Les Paralysies et Névralgies Épidémiques.

Par

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(Ce travail est parvenu à la rédaction le 17 juin 1947.)

Généralités. — On tend de plus en plus à considérer que, dans les maladies appartenant au système nerveux périphérique, tout le neurone périphérique est intéressé depuis le centre médullaire, les racines et les ganglions rachidiens, jusqu'aux nerfs périphériques eux-mêmes: ce serait une véritable *neuronite*.

Les maladies neurotropes évoluant sous forme épidémique, ont apporté un appui sérieux à cette conception moderne: et nous avons été parmi les premiers avec Henri Verger à en poser les jalons, en prenant comme exemple l'encéphalomyélite épidémique. C'est pourquoi, il nous paraît intéressant d'étudier ici dans une vue d'ensemble, ce que l'on est en droit d'appeler les névralgies et paralysies épidémiques.

Cependant, il importe de préciser qu'il ne peut s'agir alors, comme dans les méningites, encéphalites et myélites épidémiques, que d'une classification étiologique. C'est dire qu'il faudra la décomposer, si on veut s'y reconnaître symptomatiquement, en ses éléments constitutifs: et considérer les signes qui sont propres aux racines, aux ganglions et aux nerfs, en totalité ou en partie, pour en déduire les formes particulières de radiculite, de zona, ou de névrite qui caractérisent les types pathologiques en présence desquels on se trouve.

Mais si cette discrimination sémiologique est indispensable à la base, la notion épidémique qui relie ces types différents les uns aux autres n'en est que plus remarquable: elle fera l'objet de ce travail.

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La loi des séries est bien connue des médecins. Les neurologistes eux-mêmes ne l'ignorent pas. Combien de fois nous est-il arrivé aux uns et aux autres de dire, en voyant venir à notre consultation de cabinet ou d'hôpital, une paralysie faciale, un zona, une sciatique: «C'est le premier cas de l'année; il y a bien des chances que nous en observions bientôt quelques autres». Et en effet, dans les jours et les semaines qui suivaient, plusieurs cas de paralysie faciale, ou de zona, ou de sciatique tombaient sous nos yeux.

Mais on peut bien dire aussi que cette «loi des séries» n'avait guère suscité en neurologie l'idée d'épidémie, parce que pendant longtemps, sans doute, les maladies des centres nerveux parurent être d'un domaine tout à fait étranger aux toxi-infections.

Cette conception nouvelle se relie incontestablement à l'histoire de l'encéphalomyélite épidémique ou encéphalite léthargique.

Nous avons signalé en 1920—1921, au cours de notre rapport sur l'encéphalomyélite à Bordeaux et dans le Sud-Ouest, des formes névralgiques violentes se localisant notamment sur la face et au niveau du trijumeau; et d'autre part, à la même époque, certaines amauroses survenant en série nous avaient frappé, et aussi certaines paralysies de type paraplégique, dont Henri Verger avait fait l'objet d'une étude publiée par Brémaud dans sa thèse en 1920.

En février 1924, H. Verger posait, pour la première fois, la question des névralgies épidémiques. En 1926, à propos de notre article écrit en collaboration avec lui sur les «Formes basses de l'encéphalomyélite», nous discutons les formes isolées de myélites, radiculites, polynévrites. En octobre 1929, Henri Verger revenait de nouveau sur la question dans un article sur les paralysies épidémiques.

Aujourd'hui, les relations de ces névralgies et de ces paralysies sont admises et rapprochées sous une influence épidémique. Elles sont tout à fait d'actualité depuis que les épidémies de maladie de Medin sont devenues plus fréquentes et plus étendues. Car on se demande si les virus neurotropes qui sont en cause dans ces épidémies neurologiques, appartiennent à la maladie de Medin, qui est la pourvoyeuse la plus habituelle de la poliomyélite antérieure ou paralysie infantile; ou à la maladie de Cruchet, qui est l'encéphalomyélite, encéphalite léthargique ou névraxite; ou à d'autres virus qu'on n'a pu encore déterminer. C'est cette question qu'il nous faut étudier: nous commencerons par les paralysies.

Les paralysies épidémiques.

A certaines époques, on voit apparaître en série des épidémies disséminées de paralysies localisées.

Les premières qui furent observées sous ce jour étaient des paralysies rappelant beaucoup les paralysies inférieures de la diphtérie. Nous les avons considérées, avec Henri Verger, en 1926, dans notre article de la *Presse Médicale*, comme étant le plus souvent des myélites. Cependant il n'est pas douteux que certains auteurs, tels Bériel et Devic, les classent dans les polynévrites, tandis que d'autres en font de véritables neuronites (Grasset), dans lesquelles sont associés des symptômes à la fois médullaires, radiculaires et névritiques. C'est évidemment le propre des infections neurotropes plus spécialement épidémiques, de frapper les diverses parties de l'axe cérébrospinal.

Ces paralysies inférieures, bien étudiées d'abord par H. Verger et Brémaud, Cruchet, Bériel et Devic, Caillibaud, puis Ardin-Delteil, Louis Ramond, H. Schoeffer, se présentent sous une forme de polynévrite très atténuée, c'est-à-dire qu'elles sont flasques avec abolition des réflexes tendineux et des réflexes cutanés abdominaux; les masses musculaires sont douloureuses à la pression, mais molles sans atrophie, et les réactions électriques, affaiblies quantitativement, ne montrent pas la réaction de dégénérescence. Les troubles de la sensibilité objective sont insignifiants ou nuls, et les sphincters ne sont pas atteints. L'examen du liquide céphalo-rachidien est normal au point de vue cytologique et teneur en glucose; on note seulement une hyperalbuminose généralement au-dessous de 1 gramme, pouvant aller très exceptionnellement jusqu'à 6 grammes (H. Verger): c'est la dissociation albumino-cytologique.

Le début de ces accidents paralytiques est toujours soudain; ils surprennent le sujet en pleine santé, sans cause connue, ni froid, ni compression, et s'installent rapidement en quelques heures; la fièvre est exceptionnelle et on note rarement de la céphalée, des troubles digestifs. Le plus souvent, comme dans les trois cas signalés par H. Verger: une servante, balayant le trottoir, comme elle le faisait tous les matins, s'aperçoit que ses jambes ne peuvent plus la porter; ou bien un homme, en sciant du bois, se sent brusquement incapable de continuer; ou encore un chauffeur, en conduisant son auto, constate qu'il n'a plus la force de presser la poire de son avertisseur.

Des cas analogues m'ont été signalés par mes collègues argentins et uruguayens. En voici un qui m'est personnel et dans lequel il n'est pas douteux qu'il n'existe pas simplement des signes de polynévrite — comme le diagnostic en avait été formulé tout d'abord.

J'ai vu le 19 juin 1943, avec le Dr. Waldorp, le Dr. Alejandro A. X., 30 ans, pris le dimanche 6 juin, en jouant au golf, de crampes douloureuses dans la jambe gauche, puis droite et de difficulté de la marche. Il est obligé d'interrompre la partie et rentre chez lui en boitant. Les signes de paralysie augmentent et il marche de plus en plus difficilement, en steppant à travers sa chambre. Il éprouve de la gêne pour uriner, pendant deux jours.

On pense à la polynévrite à cause des crampes douloureuses et l'abolition des réflexes rotuliens et achilléens. Puis le bras droit présente aussi quelques crampes, et ensuite la jambe, mais ces signes sont passagers.

La ponction lombaire montre un peu d'hypertension, mais elle est négative à tous les examens: 0.15 d'albumine, absence de réaction colloïdale (au Lange et au Guillain). Le sang, de même que les urines, donnent des résultats normaux. Réaction de Bordet-Wassermann négative. En quelques jours l'amélioration est rapide. Plus de crampes ni douleurs paresthésiques, ou à la palpation des masses musculaires; le steppage s'atténue peu à peu.

Examen: pas d'atrophie des jambes, mollet un peu mou à gauche. Pas de réflexe achilléen ni d'extension des orteils. Pas de réflexes abdominaux, les réflexes rotuliens sont un peu vifs des deux côtés, avec ébauche de clonus de la rotule gauche. Les réflexes tendineux des poignets sont un peu vifs. Le malade se plaint d'avoir moins de force aux mains; une certaine gêne pour attraper les objets: mais il distingue tous ceux qu'on lui met dans la main, les yeux fermés; et il n'a pas de troubles de sensibilité; il reconnaît nettement, sans hésitation, ronds et croix, piqûres, température froide et chaude, sur les diverses parties des membres et du corps. La marche est presque normale avec une très légère tendance au steppage. Pas de Romberg. Pas de dysmétrie des membres supérieurs. Il y aurait eu un peu de pharyngite au début, mais sans la moindre parésie du voile du palais.

La guérison était complète quelques semaines plus tard.

Il peut arriver que la paralysie, surtout marquée aux membres inférieurs, intéresse aussi les membres supérieurs et même les muscles de la tête et du cou. Souvent elle est si peu marquée au niveau de la partie haute du corps qu'elle peut passer inaperçue: il en était ainsi dans le cas du Dr. Alejandro, ci-dessus rapporté. D'autres fois, on a une véritable tétraplégie qui rappelle encore certaines paralysies consécutives à la diphtérie, lesquelles se différencient bien difficilement, au point de vue symptomatique, de la paralysie spinale antérieure subaiguë, décrite par Duchenne de Boulogne.

Ces paralysies sont irrégulières dans leur distribution, plus ou moins marquées selon les régions du corps, et affectant de préférence la disposition segmentaire de métamérie médullaire: cependant, quand les racines sont également atteintes, et à plus forte raison les nerfs périphériques, on ne retrouve pas cette disposition.

D'autres fois, les paralysies se localisent épidémiquement sur le ou les mêmes nerfs. Nous n'avons pas besoin de rappeler à ce point de vue l'électivité de certains virus neurotropes comme celui de l'encéphalomyélite épidémique pour les nerfs moteurs oculaires: moteur oculaire commun, ou externe, ou même pathétique pris isolément, en totalité ou en partie: on sait que c'est une des particularités du type léthargique de cette encéphalite. Mais ces noyaux moteurs peuvent aussi être atteints chez plusieurs sujets, en série, en dehors de toute épidémie régnante, et faire supposer la réalité de quelque virus contagieux inapparent, qui n'en agit pas moins autour de lui.

Les mêmes constatations peuvent avoir lieu aux dépens d'un autre nerf moteur — comme le facial.

Ces petites épidémies de paralysie faciale sont aujourd'hui bien connues: elles ont été signalées par H. Verger, Kissel, les auteurs sudaméricains, en particulier Victor Escardo y Anaya en 1923, à Montevideo (Uruguay), et les médecins roumains en 1928. Les médecins argentins, Dimitri, Gareiso, Fonso Gandolfo, Bazan, etc. en ont vu également un nombre important de cas, notamment au cours de l'année 1942, ainsi qu'ils ont bien voulu me le certifier.

D'autres paralysies peuvent prendre ce caractère épidémique. Par exemple, en 1929, en quelques mois, Henri Verger avait vu non seulement trois paralysies faciales, mais encore deux paralysies radiales, deux paralysies cubitales, trois paralysies du sciatique poplité externe.

Ces paralysies peuvent s'associer à d'autres paralysies: c'est ainsi que Kissel a observé une série de 7 cas de paralysie faciale, dont 4 s'accompagnaient de paralysie du moteur oculaire externe.

Mais ce qu'il y a encore de plus remarquable, et c'est là un fait bien mis en relief par Henri Verger, c'est que ces paralysies motrices se rencontrent ou s'associent avec des nucléites, radiculites ou névrites d'ordre sensitif et douloureux se manifestant en particulier par des algies et des névralgies.

Henri Verger a ainsi rapporté l'histoire de deux conjoints, faisant à quelques jours de distance, l'un une paralysie faciale et l'autre un zona. Ces paralysies faciales s'accompagnent souvent

de douleurs prémonitoires dans la région mastoïdienne (signe de Ramsay Hunt) par irritation ou inflammation du noyau de sa racine sensitive ou intermédiaire de Wrisberg, voisin du noyau moteur; on peut aussi observer des vésicules discrètes d'herpès au niveau du pavillon de l'oreille, du même côté que la paralysie, indiquant une atteinte du ganglion géniculé ou sphéno-palatin. Un sujet, atteint de zona brachial, fait une paralysie flasque du type radiculaire; chez un autre, un zona cervical coïncide avec une paralysie faciale; un troisième présente un zona scapulo-huméral associé à une paralysie radiculaire supérieure du type d'Erb.

Des faits analogues ont été signalés en Amérique du Sud, notamment en Uruguay et en Argentine.

Le Dr. Victor Escardo y Anaya, de Montevideo, a vu en 1922 un certain nombre de paralysies faciales au cours d'une poussée d'épidémie de paralysie infantile. Les unes étaient *pures*, les autres avec des paralysies des extrémités, d'autres aussi avec des phénomènes méningés.

Jean Dubourdieu, en février, mars 1939, a observé également à Montevideo une série de paralysies primitives survenant chez des sujets en excellente santé, siégeant sur les parties les plus diverses, évoluant vers la guérison en quelques semaines à quelques mois. Il a observé un cas de ptosis palpébral gauche, un cas de paralysie faciale périphérique droite, un cas d'ataxie aiguë avec diplopie et nystagmus, un cas de paraphasie, un cas de paraplégie, surtout marquée à gauche, un cas de paralysie de la main droite, deux cas de sciatique. Dans plusieurs de ces cas, il y avait association de phénomènes douloureux (paresthésies, hypoesthésies); et dans un cas, il y eut névralgie violente de la tête, de la nuque et de la région dorsolombaire avec myoclonies.

Notre collègue fit une enquête et apprit que d'autres médecins avaient aussi constaté une série de paralysies, parmi lesquelles les paralysies faciales étaient fréquentes, puisque, à la clinique neurologique du Professeur Schroeder, et dans le service du Dr. Cassinoni, on en avait observé une vingtaine de cas. D'autres cas furent signalés, de paralysies faciales associées parfois à des névraxites, méningites lymphocytaires ou méningo-radiculites.

Le professeur Schroeder a bien voulu me confirmer cette épidémie de paralysies faciales de 1939. Quelques-unes furent précédées par un hémispasme facial, et même dans quelques cas, il y eut un hémispasme primitif. Il s'agit donc de paralysies et réactions spasmodiques survenant sous forme épidémique, et parfois

associées à des réactions douloureuses et, exceptionnellement, avec quelques vésicules zostériennes.

De l'enquête à laquelle je me suis livré auprès de mes collègues pédiatres et neurologistes argentins, il résulte que des faits identiques ont été constatés en 1942—1943, au cours de l'épidémie de maladie de Medin qui a sévi à cette époque en Argentine: j'ai noté moi-même, étant alors à Buenos Ayres le nombre important de paralysies faciales, le plus souvent isolées, qui fut observé.

Ces paralysies épidémiques ont pour caractères essentiels:

1°) D'avoir un début soudain, généralement sans fièvre, chez un sujet jusque là bien portant; de suivre une évolution rapidement favorable et de guérir complètement, presque toujours dans l'espace de quelques jours à quelques semaines.

2°) D'être des paralysies rarement limitées à un seul nerf. Par exemple, dans les paralysies radiales, il n'y a pas que les extenseurs qui sont atteints: les fléchisseurs le sont également, ce dont on se rend compte en prenant la précaution classique de relever la main, pour leur permettre de se contracter — ce qu'ils font mal. Dans les paralysies des extenseurs du pied, il y a aussi parésie des fléchisseurs et abolition du réflexe achilléen. Dans les paralysies cubitales, il y a déficit des muscles innervés par le médian (H. Verger).

3°) De s'associer à des troubles sensitifs et douloureux sous forme de paresthésies ou d'algies et de névralgies, soit spontanées, soit consécutives à la pression des masses musculaires, sans atrophie ni réaction de dégénérescence neuromusculaire.

4°) De ne s'expliquer par aucune des causes le plus habituellement incriminées — notamment le froid, les traumatismes ou la compression. La loi en série qui les régit est en faveur d'un processus épidémique.

Quand ces paralysies sont observées au cours d'une épidémie régnante, il est assez naturel de les lui rapporter, bien que la seule preuve réelle serait la preuve biologique — qui manque le plus souvent.

En vertu de l'ambiance épidémique, le virus de la maladie de Medin a été incriminé pour les paralysies isolées et notamment les paralysies faciales pures observées par V. Escardo y Anaya en 1922, et les auteurs argentins en 1942—1943.

Pour Henri Verger, ces paralysies épidémiques ont une évolution analogue à celle du zona, et aussi à ces paraplégies bénignes qu'il a décrites en 1920 avec Brémaud, et il les apparente à la maladie

de Cruchet. C'est également l'opinion de Tinel depuis 1925, et celle de Jean Dubourdien (de Montevideo) dans son mémoire de 1940 — pour ne citer que ces deux auteurs.

En réalité, les épidémies neurotropes sont vraisemblablement plus nombreuses qu'on ne croit; et si l'on parle surtout des maladies de Medin et de Cruchet, c'est parce que ce sont elles qui ont été le mieux étudiées jusqu'ici: mais il est probable que les paralysies épidémiques, si on peut les rapporter à ces deux origines pour certaines d'entre elles, sont dues aussi à d'autres virus neurotropes — jusqu'ici inconnus.

5°) En conclusion, les paralysies épidémiques sont constituées par une neuronite sensitivomotrice périphérique, dans laquelle les troubles moteurs dominant et les troubles sensitifs ne sont que secondaires et accessoires.

Les névralgies épidémiques.

La question des épidémies neurotropes, nous l'avons vu, a été pour la première fois posée par H. Verger, en 1924, à l'occasion des névralgies.

Frappé depuis 1914 de l'augmentation des névralgies, qui survenaient en série, l'éminent neurologue bordelais avait étudié ces faits de plus près et s'était aperçu que ces névralgies s'éloignaient par leur début, leur évolution et leurs causes, de celles jusque-là décrites.

Leur début est brusque, sans fièvre ni malaise en général, et sans qu'on puisse invoquer le froid, la fatigue ou quelque infection banale, telle la grippe. Comme ces douleurs sont fréquemment nocturnes, on pense à la syphilis, mais on ne constate aucun antécédent suspect et toutes les recherches biologiques, à commencer par la réaction de Bordet-Wassermann, sont négatives.

Quels sont les caractères cliniques de ces névralgies? Chez les jeunes ou les vieux, hommes ou femmes, des douleurs apparaissent dans le membre supérieur ou la région cervico-céphalique, d'autres fois au niveau des espaces intercostaux, du tronc, du dos ou du membre inférieur; ce sont des douleurs vives, parfois intolérables. à paroxysmes plus ou moins longs laissant dans leur intervalle un endolorissement diffus pénible, la nuit comme le jour, à prédominance nocturne. Les mouvements sont habituellement sans action sur la douleur.

L'un place sa main au-dessus de la tête pour soulager la crise

douloureuse du membre supérieur; l'autre arpente sa chambre quand la crise survient, la nuit, pour atténuer les douleurs au niveau de son membre inférieur. Mais les crises sont si pénibles que rien ne les arrête, que le sujet doit interrompre ses occupations et que le sommeil lui-même, non seulement ne les calme pas, mais est remplacé par de l'insomnie.

Il est presque toujours impossible pour le malade de localiser les points exacts au niveau desquels il souffre: la région dont il se plaint ne présente aucune manifestation visible et n'est pas douloureuse au contact, à la pression. Les troncs nerveux eux-mêmes sont indolores. La topographie en est imprécise, car la douleur ne suit pas le trajet d'un nerf déterminé. Chez celui-ci, qui a 60 ans, c'est la moitié gauche du crâne, de la face, de la partie supérieure du cou qui est prise; chez celui-là, âgé de 45 ans, le bord externe du bras et de l'avant-bras; chez ce troisième, qui a 40 ans, la partie postérieure du mollet et de la malléole externe: mais chez tous, c'est plutôt une indication régionale qu'une localisation véritable.

Le froid est sans action; par contre les efforts, la toux, l'éternuement, sont susceptibles de déclencher des paroxysmes douloureux.

La sensibilité à la piqure paraît cependant diminuée dans les lieux correspondant aux zones douloureuses, mais sur un territoire plus restreint qui affecte, au niveau des membres, la distribution de bandes parallèles à l'axe.

Il n'existe pas d'impotence motrice, ni d'atrophie musculaire. Les réflexes tendineux et périostés sont diminués dans les zones algiques. On note parfois quelques phénomènes vasomoteurs: oedème au pied ou à la main, à un seul doigt.

Ces crises névralgiques pénibles atteignent rapidement en quelques jours leur acmé; puis elles s'apaisent progressivement, laissant toutefois des sensations paresthésiques désagréables, notamment au niveau des doigts; et disparaissent complètement en quelques semaines à un ou deux mois, plus exceptionnellement en trois ou quatre mois (17 mois dans un cas de H. Verger).

Durant l'hiver 1930—1931, j'ai été consulté pour des algies survenant en série, et du même type.

J'ai vu notamment une dame âgée de 44 ans qui avait été prise brusquement, une nuit de mars, de douleurs violentes dans le membre supérieur droit. Ces douleurs encerclaient le poignet, écrasé comme dans un étau de fer, et remontaient le long du bord postérieur de l'avant-bras, puis du bras, et s'irradiaient jusque dans la région cervicale, vers la

4^{ème} cervicale. La pression le long des nerfs et des masses musculaires ne modifiait en rien ces douleurs, sauf au niveau de la région cervicale où la pression forte provoquait une sensation pénible. Le plexus cervical était également douloureux au toucher dans la région sus-claviculaire. La malade accusait quelques fourmillements au niveau de l'annulaire, du médus et de l'auriculaire de la main droite. Mais la sensibilité objective était absolument normale sous tous ses nodes. Il n'existait aucun trouble trophique. Les réflexes étaient normaux.

Pas le moindre trouble moteur d'ordre paralytique. La malade se plaignait toutefois de ressentir, à certains moments, quelques frémissements vermiculaires passagers le long des muscles de l'avant-bras et de la cuisse du côté droit. Ces douleurs intolérables n'étaient guère calmées que par l'opium et la morphine.

Je pensais à une poliomyélite cervicale postérieure ou sensitive, dont l'allure épidémique était frappante, étant donné les autres formes névralgiques analogues qui étaient signalées à la même époque. D'ailleurs aucune cause nette n'était en jeu: ni la syphilis, ni aucune intoxication, ni le froid, ni le traumatisme.

Je conseillai en conséquence un traitement par la méthode phylactison en moins de quinze jours. Cette malade, qui a aujourd'hui 60 ans, n'a jamais eu d'autre crise depuis.

Henri Verger avait été justement frappé de la physionomie radiculaire de ces algies: car on ne retrouvait pas nettement chez elles ni les douleurs de pression aux points de Valleix, ni les douleurs sur le trajet des nerfs, tandis qu'elles s'exagéraient dans les efforts. D'autre part, ces épidémies neurotropes disséminées, sans contagion directe, lui rappelaient trait pour trait les épidémies zostériennes, à cette différence près qu'on constatait leurs caractères symptomatiques et évolutifs, mais sans l'éruption elle-même. Si bien qu'on ne pouvait s'empêcher de penser à ces zones sans éruption (de Sicard et Minet), pour lesquels, si le terme de zone ne saurait être, à mon avis, accepté, il n'en restait pas moins les signes évidents de radiculite postérieure: et c'est là l'essentiel.

Cependant il serait exagéré de localiser les épidémies algiques aux seules racines postérieures. Si les radiculites en constituent une des formes les plus fréquentes, pour lesquels, si le terme de zone groupe toutes les autres algies, qu'elles soient exclusivement ganglionnaires, tronculaires ou funiculaires.

L'expérience nous a démontré que la même variabilité dans la localisation des voies motrices périphériques se rencontre dans la localisation des voies sensitives périphériques. J'ai connu des malades atteints en série, selon les cas, d'algies de la face, du cou et de l'épaule (torticolis douloureux), du bras

et de l'avant-bras, du dos ou des lombes, des fesses, de la jambe ou du pied, et dont les douleurs n'avaient aucun caractère radiculaire.

Je me souviens en particulier d'une sténo-dactylo, de 65 ans, qui fut prise brusquement, une nuit, de douleurs névralgiques qui ne lui laissaient aucun répit, tant elles étaient pénibles. Au repos complet, elle ne souffrait presque pas; mais le moindre mouvement lui tirait des cris de douleur.

J'ai connu d'autres malades chez lesquels *certain*s mouvements étaient seulement douloureux. Pour aller d'une position à l'autre, il y avait «une zone dangereuse» à traverser, en deçà et en delà de laquelle tout allait bien.

Le pis est pour le médecin, dans les cas de ce genre, qu'il lui est impossible de localiser exactement le point douloureux: ni les racines, ni les troncs ou filets nerveux, ni les articulations, ni les masses musculaires ne sont capables de permettre par leur examen la détermination de la souffrance qui, cependant, est extrême, bien qu'elle ne dure que quelques instants.

L'évolution suit alors presque toujours le même rythme: la douleur survient brusquement, sans cause nettement déterminée, puis augmente petit à petit pendant 8 à 15 et 30 jours, selon les cas; puis elle régresse ensuite en un temps sensiblement égal, pour disparaître complètement.

La seule chose évidente est l'allure épidémique de ces algies — qu'on appelle parfois «rhumatismales», faute de mieux — et qui, aux mêmes époques, frappent des individus différents et sous les types les plus divers: névralgies de la tête et du cou, de l'épaule, des espaces intercostaux, lombagos, sciatiques, métatarsalgies etc.

De ces formes névralgiques, il faut rapprocher ce qu'on a appelé la *pleurodynie épidémique*, encore dénommée myalgie ou diaphragmalgie épidémique, grippe de Devil, maladie de Bornholm. Signalée d'abord en Islande en 1856, elle a été observée en Nord-Amérique par Dahney, en 1888, et par Reilly en 1921, et aussi en Suède, Norvège et Finlande.

Les auteurs américains en font une maladie à virus neurotrope qui se rencontrerait dans les sécrétions du nasopharynx, dont les filtrats seraient virulents. Elle se montre sous forme de petites épidémies printanières, plus chez les jeunes que chez les gens âgés. Elle se transmettrait par la salive et les mains.

Début foudroyant par mal de tête, langue saburrale, parfois vomissements et diarrhée, pharyngite, et par des symptômes extrêmement douloureux. La douleur, localisée au niveau des

insertions du diaphragme, se manifeste sous forme de piqûres, d'arrachements ou de pression; elle s'exagère dans tous les mouvements thoraciques, la toux, les éternuements, le hoquet; la respiration est superficielle, car dans les inspirations profondes la douleur devient intolérable, ce qui oblige le patient à immobiliser le thorax le plus qu'il peut.

Les douleurs peuvent s'irradier dans les bras, dans les lombes et dans les jambes, et surtout au niveau de la tête.

La fièvre accompagne les douleurs; elle s'élève à 39° ou 40°, mais ne dure qu'un jour ou deux. Au bout de quelques jours à 8 ou 10 jours, la guérison est généralement obtenue, sans complications, sauf dans quelques cas où l'on a observé une pleurésie fibrineuse.

Tous les appareils sont normaux; en particulier l'examen des urines et la radiographie pulmonaire sont négatifs. On a mentionné de l'éosinophilie dans le sang au moment de la convalescence.

On voit par ce rapide aperçu que les épidémies algiques périphériques sont extrêmement variées.

Un autre de leurs caractères, sans doute le plus remarquable, est de s'associer souvent à des paralysies, de même que celles-ci, quand elles sont épidémiques, s'associent à des phénomènes fréquemment douloureux, ainsi que nous l'avons vu.

Cependant, au cas de névralgies épidémiques, ce sont les phénomènes douloureux qui dominent le tableau clinique, et les phénomènes paralytiques, quand on les rencontre, ne sont que secondaires et accessoires.

Il n'en est pas moins vrai, en conclusion, que cette association sensitivomotrice épidémique donne, quand elle existe, sa physiologie la plus originale à ces épidémies neurotropes périphériques.

Considérations générales et thérapeutiques.

Ce qui domine le chapitre des paralysies et des névralgies épidémiques c'est cette notion du «génie épidémique» des vieux auteurs, qui est toujours aussi vraie qu'au premier jour.

De ce génie appliqué à l'épidémicité neurotrophe on connaît deux variétés pathologiques qui ont été le plus particulièrement étudiées: la maladie de Médin et la maladie de Cruchet.

A notre avis, ce n'est d'ailleurs que l'ouverture d'un nouveau chapitre, car les virus neurotropes ne sont encore qu'au commencement de leur histoire biologique. Ils sont certainement beaucoup

plus nombreux qu'on ne pourrait le croire; et les méningites, les encéphalites, les myélites et les radiculites ne sont que les localisations de leur mauvais génie extrêmement polymorphe.

Il est probable que de ces virus neurotropes les uns sont susceptibles de provoquer des réactions générales de défense de l'organisme avec la fièvre, et les autres, non; il est vraisemblable que les mêmes, selon leur degré de virulence, peuvent donner naissance à ces deux ordres de phénomènes contraires. A ce point de vue, nous savons encore bien peu de ces virus neurotropes, qui ont cependant produit des travaux déjà considérables en ce qui concerne plus spécialement la poliomyélite épidémique, ou maladie de Medin, et l'encéphalomyélite épidémique, ou maladie de Cruchet.

Il est possible que ces maladies épidémiques soient dues à des virus filtrants différents. La question s'est posée nettement pour la maladie de Cruchet à propos des encéphalomyélites japonaise, nordaméricaine et australienne qui seraient causées par un virus filtrant spécial.

Le problème est identique en ce qui concerne la maladie de Medin: peut-on assurer que le virus filtrant qui lui donne naissance est le même dans tous les cas considérés?

Il y a, en plus, d'autres virus déjà étudiés, dus à l'herpès, au zona. On sait également que certaines réactions neurotropes rencontrées dans la varicelle, la rougeole, la coqueluche, la variole, la vaccine, le rhumatisme articulaire aigu, etc., etc., seraient dues à des virus filtrants non encore déterminés.

Comment agir contre tous ces virus? Pour lutter efficacement contre leurs méfaits, il faudrait d'abord les connaître, et les différencier les uns des autres. Or, on est encore loin d'en être arrivé à. Si pour certains d'entre eux, on a pu réussir par des microscopes renforceurs, grâce à des grossissements jusque-là impossibles, à pouvoir les déceler, on en est resté pour les combattre, à une thérapeutique essentiellement symptomatique.

Au cours d'une épidémie de maladie de Medin, il sera indiqué de traiter ces paralysies et névralgies épidémiques par la sérothérapie antipoliomyélitique, et en particulier le sérum de Pettit, ou les sérums analogues; à leur défaut, on pourra utiliser le sérum de convalescent.

Mais ses sérums sont loin d'avoir une action efficace, si bien qu'on leur adjoint d'autres médicaments: vitamine B1, sulfamides, et même pénicilline, pour ne citer que les plus récents utilisés.

Je me permettrai d'attirer l'attention sur la méthode *phylactique*, que je préconise depuis 1930. Elle est basée sur les recherches expérimentales de Billard qui ont démontré que certaines substances virulentes ou toxiques avaient un pouvoir protecteur contre les toxines neurotropes, de quelle que nature qu'elles soient. Parmi ces substances protectrices, nous avons signalé avec Noblia le salicylate de soude, l'uroformine, l'alcool, le somnifène, le gardénal, et surtout le chloroforme, que nous avons plus particulièrement étudié.

Les substances phylactiques se fixent sur les cellules nerveuses dont elles chassent le virus, qui est remis dans la circulation. Il suffit alors de favoriser l'élimination de ce virus par l'injection d'un sérum spécifique ou, si l'on n'en a pas, par l'injection d'un sérum provenant de préférence d'un convalescent de la maladie que l'on traite, parce qu'il est plus actif, ou encore par l'injection d'un antitoxique — telle la septicémine par exemple. Et l'on obtient des résultats remarquables.

Le traitement du tétanos par l'anesthésie chloroformique est une démonstration caractéristique de cette méthode. Le chloroforme chasse la toxine tétanique des centres nerveux; et celle-ci, fixée par le sérum antitétanique injecté, est éliminée par les émonctoires.

Nous avons appliqué la même méthode aux paralysies diphtériques; et nous l'avons étendue aux paralysies et névralgies épidémiques.

En ce cas, comme dans celui de M^{me} D., cité plus haut, nous avons employé le gardénal comme substance phylactique et injecté de la septicémine en injections intramusculaires pour agir sur le virus mis en liberté, et l'éliminer.

D'autres fois nous avons utilisé le somnifène, ou le chloroforme, ou l'alcool, ou le salicylate de soude, etc., comme substance phylactique, tandis que nous injectons du sérum de convalescent, ou un agent colloïdal comme moyens de désintoxication et d'évacuation de la toxine libérée.

Il est possible que la pénicilline puisse agir dans le même sens; mais nous n'en avons pas l'expérience à ce point de vue.

On voit, en conclusion, le grand intérêt soulevé par cette question encore peu connue des paralysies et des névralgies épidémiques.

Summary.

1. Cases of peripheral paralysis and neuralgia may appear in the form of an epidemic.

2. This idea, suspected during the great epidemic of encephalomyelitis in 1920—1921 at l'Ecole bordelaise, was clearly formulated there in 1924, 1926 and 1929 (H. Verger and R. Cruchet).

3. The neurotropic virus of these paralyzes and neuralgias have been most frequently reported in cases of epidemic poliomyelitis, or Medin's disease, and in epidemic encephalomyelitis or Cruchet's disease; but it is certain that many other filtrable viruses might give rise to them.

4. Among the treatments initiated, R. Cruchet draws attention to the *phylactic* method, which he has studied especially since 1930, and which may give remarkable results.

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On Individual Variations in Serum Cholesterol.

By

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Although the deposition of lipids and especially cholesterol in arterial walls is a characteristic finding in case of arteriosclerosis, there is nevertheless no constant relation between serum cholesterol values and the frequency or gravity of arteriosclerosis in different diseases as for instance diabetes mellitus (10,13). Moreover, there is no parallelism between the content of cholesterol in aorta and the concentration of cholesterol in serum, as long as the latter quantity lies within its normal limits; however, a hypercholesterolemia entails an increased amount of cholesterol in aorta (6). Whatever the mechanism involved in the deposition of cholesterol in the arterial walls may be, there is, from general principles of physical chemistry, hardly any doubt that high concentrations of cholesterol in serum will favour the deposition. It is therefore of considerable interest, if it should be possible, by therapeutic measures, to reduce the concentration of cholesterol in serum.

American workers have reported that administration of choline entails a decrease in serum cholesterol. Hermann has shown this in experiments on hens (7), and he has also found lower values of serum cholesterol in man after administration of choline for some time (8). The explanation of this may be somehow connected with the ability of choline to prevent the formation of fatty liver, although experimentally no relation has been found

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between the fat content in the liver and the concentration of cholesterol in serum in states in which there is an accumulation of fat in the liver cells.

In Rigshospitalets Medicinske Afdeling B we have in various ways attempted to reduce the serum cholesterol in patients with hypercholesterolemia. The results of this work will be communicated later. However, in order to be able to value it properly, we found it reasonable first to examine the variations in serum cholesterol in patients who had undergone no treatment in order to reduce their serum cholesterol.

Previous investigations, which have been carried out with good analytical methods, of the variations in serum cholesterol in normal adults over shorter or longer time intervals — hours, days, weeks, months — have shown that the values obtained are roughly constant and deviate at most 15 % from the average (2, 3, 14). Though some workers (11), using imperfect analytical methods and studying only relatively few subjects, have found somewhat greater variations, it must on the whole be regarded as established that the variations in one and the same individual are fairly small. There is no definite dependence on such factors as intake of ordinary food, sleep, time of day for drawing of blood samples, sex and age (2, 5, 9, 14).

In patients with various diseases it has been found that the variations in one and the same individual are small. They are in general of the same order of magnitude as in normal subjects and far smaller than the variations from one individual to another (12, 15).

New Investigations.

Serum cholesterol was determined by the procedure described by Brun (4). This is a modification of the method of Schönheimer and Sperry, and involves a precipitation with digitonine and careful washing of the precipitate with ether. Though the method is very time consuming, we have preferred it on account of its accuracy. Thus the standard deviation was found to be around 1 %. Double analyses were always carried out.

The investigations were carried out in the fall of 1946 and during the winter 1946—47. Our material includes all the patients, all in all 79, on whom for diagnostical or other reasons a cholesterol

Table 1.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the grouping of the patients according to the nature of their diseases.

Difference between serum cholesterol values in mg %	$\begin{smallmatrix} + \div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} + \div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \div \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ > \\ 100 \end{smallmatrix}$	Total
<i>Nature of disease</i>										
Arteriosclerotic heart diseases	3	2	1	2	4		2	4	3	21
Other heart diseases				3	1			3		7
Hypertension arterialis	3		1		2		4	4		14
Lung diseases				1						1
Kidney diseases						1	2		1	4
Liver diseases	1	3	1		2		1		1	9
Diseases of stomach and intestine							1	1		2
Nervous diseases	2			3				1		6
Endocrine and metabolic diseases	3	2		2			1		4	12
Diseases of the blood	1				1					2
Muscular diseases							1			1
										79

determination was carried out. In 35 patients 2 cholesterol determinations were carried out, in 22 patients 3 determinations and in 22 patients from 4 to 10 determinations. A cholesterol determination was carried out every week. Samples of venous blood were drawn in the morning, before the patients had got any food.

The first determination was carried out a few days after the patients' being admitted to our hospital department. In all tables below, except in Table 8, this first determination forms the basis of the comparisons, since we had a particular interest in investigating whether the stay in hospital and the treatment there affected the cholesterol values.

Each table contains 3 main divisions designated by +, - or \pm ; + indicates that all cholesterol values were higher than

the first, — that all were lower, and \pm that some were lower and some higher. The subdivisions give the magnitude of the variations in mg %, so that the greatest deviation from the first value determines the classification independent of the time relations.

It appears from Table 1 that 23 patients showed fluctuating, 22 showed increasing and 34 showed decreasing cholesterol values during their stay in hospital. Although the numbers are relatively small, there can hardly be any doubt that the tendency towards decreasing values is preponderant. A subdivision of the three main groups with variations from 0—50 mg % into 2×3 groups with variations from 0—25 and 25—50 mg % respectively showed a distribution of 22 patients in the first and 14 patients in the second group. All in all 36 patients showed variations from 0—50 mg %, 30 variations from 50—100 mg % and 13 variations greater than 100 mg %. In the latter group 9 patients showed a decrease in their cholesterol values.

In Table 1 the material has also been arranged according to the nature of the diseases. It appears that a large part of our patients, 42 out of 79, are suffering from circulatory disturbances. Of these 20 suffered from coronary sclerosis. The number of patients with diseases in other organs is therefore relatively small. Our material therefore cannot be regarded as a representative average for a medical department. This is mainly due to the circumstance that our department takes a particular interest in the relation of cholesterol to heart diseases, especially coronary sclerosis. With the exception of a case of e. hepatitis none of our patients had malignant tumors.

It can be concluded with a fair degree of certainty that there are no constant relations between cholesterol variations and arteriosclerotic heart diseases. The number of patients in the other groups is too small to allow definite conclusions to be drawn. However, it appears probable that no constant relations to cholesterol variations can be found.

It appears from Tables 2 and 3 that there is no definite relationship between the sex, age and weight of the patients and the variations in cholesterol values. In particular, there is no difference between young patients, from 20 to 50 years, and old ones.

Changes in weight (Table 4) have no definite relation to changes in cholesterol. The loss of weight is in some patients due to the excretion of edematous fluid; in these patients, which very often

Table 2.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the grouping of the patients according to age and sex.

Difference between serum cholesterol values in mg %	$\frac{+}{0-50}$	$\frac{+}{50-100}$	$\frac{+}{>100}$	$\frac{+}{0-50}$	$\frac{+}{50-100}$	$\frac{+}{>100}$	$\frac{\div}{0-50}$	$\frac{\div}{50-100}$	$\frac{\div}{>100}$	Total
<i>Age of patients</i>										
20-30 years ..	1	2		1	1		1		1	7
30-40 years ..		1		3	2		3			11
40-50 years ..	3	1	1	3	3		1	2	1	15
50-60 years ..	3	2	2		1	1	4	5	5	23
60-70 years ..	5	1		3	2		2	3		16
70-80 years ..	1			1	1		1	1	2	7
<i>Number of</i>										
female patients	3	1	2	6	7	1	8	6	5	39
male patients..	10	6	1	5	3		4	7	4	40

Table 3.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the grouping of the patients according to weight.

Difference between serum cholesterol values in mg %	$\frac{+}{0-50}$	$\frac{+}{50-100}$	$\frac{+}{>100}$	$\frac{+}{0-50}$	$\frac{+}{50-100}$	$\frac{+}{>100}$	$\frac{\div}{0-50}$	$\frac{\div}{50-100}$	$\frac{\div}{>100}$	Total
<i>Weight in kg.</i>										
40-50.....				1	3					6
50-60.....	3		2	2	2		1	1	1	12
60-70.....	5	5		6	3	1	5	4	5	34
70-80....	4	1	1		1		3	4	2	16
80-90.....		1		1	1		2	2		7
90-100.....				1			1			2
>100.....	1							1		2

showed stasis of the liver, the cholesterol did not show constant variations or particularly low values.

The treatment with a diet low in calories seems on the whole to reduce the cholesterol values, as will appear from Table 5. 14 out of 18 patients receiving this diet showed decreasing cholesterol values. This is in conflict with the fact that there is no definite relationship between cholesterol values and loss of weight; however, the results may be masked by a loss of weight caused by excretion of edematic fluid. There is only a slight difference between the full diet and the restricted hospital diet,

Table 4.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the grouping of the patients according to the changes in weight during their stay in hospital.

Difference between serum cholesterol values in mg %	$\begin{smallmatrix} +\div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ > \\ 100 \end{smallmatrix}$	Total
<i>Changes in weight.</i>										
+ — 1 kg	8	2		6	4	1	4	6	4	35
+ 1—3 kg	2	1	1				2			6
+ 3—5 kg		1		2			1			4
+ 5—10 kg ...			1		1					2
— 1—3 kg	1	2		2	3		2	5	3	18
— 3—5 kg		1	1	1	2		2	1	1	9
— 5—10 kg ...	1							1		3
— > 10 kg	1						1			2

Table 5.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the grouping of the patients according to diet.

Difference between serum cholesterol values in mg %	$\begin{smallmatrix} +\div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ > \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 0- \\ 50 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 50- \\ 100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ > \\ 100 \end{smallmatrix}$	Total
<i>Diet.</i>										
Full diet.....	12	5	3	9	9	1	5	5	4	53
Restricted diet.								2	3	5
Full diet + extra								1		1
Full diet in small portions		1		1			4	3	2	11
Reducing diet	1				1		3	2		7
Full diet ÷ sugar		1		1						2

and it is therefore hardly of any importance that 5 patients receiving the restricted diet showed a decrease in their cholesterol values.

24 patients received a treatment in the form of massage, various baths, carbon arc light or X-ray irradiation without any constant changes in the cholesterol values.

Table 6 shows the effect of various drugs on the cholesterol values. Only the most frequent forms of treatment have been taken into consideration, namely digitalis, theobromine, phenemal

Table 6.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the treatment received during stay in hospital.

Difference between serum cholesterol values in mg %	$\begin{smallmatrix} +\div \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ >100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ >100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ >100 \end{smallmatrix}$	Total
<i>Drug.</i>										
Digitalis	2				1		3	1	1	8
Theobromine ..	5		1	6	2		7	5	3	29
Allypropynal ..	8	1	2	8	6	1	8	5	4	43
Phenemal mites	1	1	1	1	4		3	6	2	19
Paraffin oil + linseed	3	3	1		4		5	4	5	25
Magnii tartras.			1	1	3		1		1	7
Stilbestrol			1	1	1		1			4
Total:	19	5	7	17	21	1	28	21	16	135

Table 7.

Difference in serum cholesterol between the first and the subsequent determinations in relation to the initial serum cholesterol values.

Difference between serum cholesterol values in mg %	$\begin{smallmatrix} +\div \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} +\div \\ >100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} + \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} + \\ >100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 0-50 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ 50-100 \end{smallmatrix}$	$\begin{smallmatrix} \div \\ >100 \end{smallmatrix}$	Total
Initial serum cholesterol values in mg %.										
100-150	1	1		1	1					4
150-200	4	3	1	3	2					13
200-250	4			4	1		5	2		16
250-300	3	1		2	2		4	5	2	19
300-350	1	1			3		3	6	2	16
350-400		1	2	1	1	1			3	9
400-450									2	2

mites, allypropynal, paraffine oil, linseed, magnesium tartrate and stilbestrol. The drugs were given over a longer time interval, and often two or more were given within the same period; by the final enumeration of our cases one and the same patient has therefore sometimes been counted twice or even more times. There is no constant relationship between the kind of drug and the cholesterol variations. By considering the variations in cholesterol after one week of treatment with the drug in question, no definite relationship could be found. If the treatment was discon-

tinued, no marked changes were observed at the subsequent cholesterol determination. Many other drugs have also been used, but our figures are here too small to allow definite conclusions to be drawn. They are therefore omitted. It may be mentioned that three cases in which a thyreoidea treatment was given, showed a decrease in cholesterol. This is a well known fact.

We have further investigated whether confinement to bed had any effect on the cholesterol values. We have here compared with either the first cholesterol determination made at the hospital, or with the last determination made before the patient got up or was confined to bed. No effect on the cholesterol values could be demonstrated.

In Table 7 a comparison has been made between the initial values of serum cholesterol and the variations observed later. It is seen that the 17 patients with an initial value below 200 mg % did not show any decrease in serum cholesterol during their stay in hospital, but instead fluctuating or increasing values. However, 27 out of 46 patients with initial values greater than 250 mg % showed a decrease. There is therefore hardly any doubt that patients with high initial values of serum cholesterol show a tendency towards a spontaneous decrease during their stay in hospital.

There was no relationship between cholesterol variations and values of hemoglobine or sedimentation rate, or changes in these.

Of the total number of patients 24 showed so greatly varying values of serum cholesterol that the greatest deviation from the mean value of all determinations in one and the same patient was greater than 15 %. Of these patients 15 showed a decrease, 7 showed fluctuating values and only 2 an increase during their stay in hospital. In this group there is therefore a pronounced tendency to a decrease in serum cholesterol. From our material no relationship can be deduced between the diagnosis and the magnitude of the deviation (expressed in per cent). It is, however, remarkable, that of the 8 patients with the greatest deviations from the individual average, 4 suffered from hepatitis acuta 4 other patients with hepatitis acuta showed deviations smaller than 15 %.

The patient with the greatest deviation from the average value suffered from coronary sclerosis. During his stay in hospital he developed phlebitis of the lower extremities, which was treated with dicumarol. Before this treatment 4 cholesterol values

Table 8.

Statistics of patients with variations in cholesterol greater than 15 % compared with the average value.

Sex	Age	Diagnosis	Max. value	Min. value	Average	Greatest deviation from average in %	Difference between the first and the subsequent determinations in mg %
♂	60	Mb. c. aortae luic.	242	177	210	15.3	÷ 50-100
♂	53	Scler. aa. cor.	271	206	231	17.5	÷ 50-100
♂	35	Obs. f. saturnismus	300	207	253	18.0	÷ 50-100
♂	53	Hypert. art.	238	165	201	18.2	÷ 50-100
♂	74	Myxedema	291	201	246	18.4	÷ 50-100
♂	53	Hypothyreoidismus	372	256	314	18.4	÷ > 100
♂	60	Scler. aa. cor.	352	248	295	18.9	÷ > 100
♂	72	Scler. aa. cor.	322	222	271	18.9	÷ 50-100
♂	47	Thromb. aa. cor. seqv.	396	273	333	19.0	+ 50-100
♀	50	Diab. mell.	250	191	210	19.5	+ 50-100
♀	55	Nephrosis	549	399	458	19.8	+ > 100
♀	47	Mb. Simmond	499	382	416	19.9	+ > 100
♂	69	Thromb. aa. cor. seqv.	182	133	153	20.4	+ 25-50
♂	58	Porphyria chr.	329	237	271	21.4	÷ 50-100
♂	56	Scler. aa. cor.	301	197	247	21.8	÷ > 100
♂	59	Hypert. art.	292	187	232	25.5	÷ 50-100
♂	42	Hepatitis ac.	364	214	289	25.8	÷ > 100
♂	55	Mb. cord. mitr.	270	155	212	27.1	÷ > 100
♂	64	Hemorrh. cerebri	371	211	291	27.5	÷ > 100
♂	40	Hepatitis ac.	274	156	211	30.0	+ 50-100
♂	56	Hepatitis ac.	322	177	245	31.5	+ > 100
♀	31	Diarrhoea, achylia	215	125	159	35.3	÷ 50-100
♂	21	Hepatitis ac.	178	79	127	39.9	+ 50-100
♀	71	Scler. aa. cor.	332	135	235	40.9	÷ > 100

were in the neighbourhood of 300 mg %, while 3 subsequent determinations gave results about 150 mg %. The patient reacted on small doses of dicumarol with a prolonged reduction of the prothrombine time. However, two other patients, also treated with dicumarol against phlebitis, showed only small variations in cholesterol, and it is therefore unlikely that dicumarol was responsible for the great reduction in cholesterol observed in the first patient.

Discussion and Conclusion.

On account of the accuracy of our experimental procedure, it can be safely concluded from the investigation reported above that the serum cholesterol values in a relatively high proportion of patients suffering from various diseases vary considerably. The variations are greater than found previously (2, 3, 12, 14, 15). This may be explained by the circumstance that we have preferred to determine serum cholesterol in patients in whom an increased concentration of cholesterol was possible or even probable, and that patients with high cholesterol values show a tendency towards greater variations than those with low values of serum cholesterol.

We have not been able to demonstrate any characteristic conditions or relationships common to all those patients that showed either fluctuating, or decreasing, or increasing values of serum cholesterol, compared to the first determinations carried out in the hospital. Like previous investigations, our work is therefore unable to give any explanation for the variations in serum cholesterol. However, it is probable that the explanation cannot be sought in changes in the intestinal absorption of cholesterol, since the variations are too heterogeneous within the same groups of patients. It is more likely that we are concerned with changes in intermediary cholesterol metabolism, or in the synthesis or breakdown of cholesterol, or perhaps in the deposition or excretion. However, our knowledge of all these processes is very superficial and completely inadequate to explain the variations. It may be mentioned that the recent discovery of the ability of the organism to synthesise cholesterol from acetic acid (1) has increased the interest in the problems of cholesterol metabolism. The synthesis may take place in the liver. As mentioned above we found in our material among the 8 patients showing the greatest variations in serum cholesterol all in all 4 with hepatitis acuta, while the other 4 did not show symptoms of any liver injury, except one who had been treated with dicumarol. This may give a hint about the rôle of the liver in cholesterol variations.

The main result of this investigation is that serum cholesterol in patients varies more than has been supposed so far. Moreover, in patients with high initial values of serum cholesterol there is a tendency to a spontaneous decrease during their stay in

hospital. This fact must be taken into consideration in estimations of the effect of a treatment which aims at the reduction of the concentration of serum cholesterol.

Summary.

1. In 79 patients the variations in serum cholesterol were studied by means of weekly determinations.

2. Compared to the serum cholesterol value immediately before admission to hospital 23 patients showed fluctuating, 22 increasing and 34 decreasing values. 24 patients had a maximum deviation from the individual average between 15 and 40 %, while 55 had a deviation smaller than 15 %.

3. Patients with high initial values of serum cholesterol had a tendency to a spontaneous decrease during their stay in hospital and showed the greatest deviations from the individual average.

4. No relationships have been found between cholesterol variations, diagnosis, sex, age, weight, diet, confinement to bed, physical therapy or treatment with such drugs as digitalis, theobromine, dormitives and laxatives. However, there seems to be a tendency to a decrease in cholesterol values in patients receiving a diet of low caloric value.

5. The possible reasons for the variations in serum cholesterol are briefly discussed, and the possible rôle of the liver as one of the factors regulating the concentration of serum cholesterol is pointed out.

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Agglutination of Hemolytic Streptococci (Group A) in Serum from Patients with Rheumatoid Arthritis.

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The theory of streptococci as the cause of rheumatoid arthritis continues to be of high importance, and since it was first advanced has been supported by serological and bacteriological investigations, including agglutination tests — more especially in the United States.

Cecil, Nicholls & Stainsby (1931) tested synovial fluid and blood from rheumatoid arthritis patients. In 62 % a streptococcus was found in the blood. It was described as a *Str. viridans* (α -hemolysis). The authors called this a »typical strain» and considered it to be the probable cause of rheumatoid arthritis. In support of their theory they showed that 94 % of sera from these patients agglutinated at a titre of ≥ 640 when this streptococcus was used as the antigen, whereas only about 2 % of control sera could agglutinate at the same titre with the same antigen. Gray & Gowen (1931) were able to verify these findings on the whole. In 64 % of cases they were able to cultivate from the blood a *Str. viridans* from patients of the same kind, but only in 8 % from a control material. These authors called the isolated *Str.* »the rheumatoid streptococcus», and for the rest considered it identical

with the »typical strain» isolated by Cecil et al. The titre in agglutination tests with sera from polyarthritis patients was found to be ≥ 640 in 62 % when this Str. was used as antigen.

As the result of a number of experiments (1931, 1932, 1934 and 1936) Dawson & Olmstead et al. demonstrated that the agglutination of Str. in sera from patients with rheumatoid arthritis was scarcely specific. Apparently the reaction could better be carried out with hemolytic Str. as antigen, even when it was a Str. viridans that had been isolated from the blood by earlier workers. The best results, however, were obtained by using haemolytic Str. of Laneefield's Group A. The authors also claimed that other bacterial antigens, including Str. viridans, were unsuitable for this reaction. They regarded a titre of ≥ 160 as a positive reaction. It was remarkable that in a material consisting of indubitable streptococci infections there were only 8 % of positive reactions.

Keefer, Myers & Oppels (1933) observed agglutination in sera from patients with rheumatoid arthritis when the antigen was hemolytic Str. The reaction was not strain-specific but dependent only upon whether the Str. were hemolytic or not.

McEwen & Alexander (1935) were able to confirm that the strongest agglutination was obtained by using hemolytic Str. of Group A as the antigen. Other groups (B, C, D, E) were also agglutinizable, however, but to not nearly the same degree. Of these other groups C gave the strongest reaction. The authors considered that this »cross-reaction» was due to some non-group-specific factor common to all hemolytic streptococci.

In 1938 Goldie found that 75 % of 28 patients with rheumatoid arthritis showed a positive agglutination reaction with hemolytic Str. with the titre of ≥ 200 . Only 5 % in a control material reacted positively. He expressed the opinion that a positive agglutination reaction was a sign of long chronic infection with hemolytic streptococci.

Packalén (1943) also used hemolytic Str. of Group A as the antigen and on the whole followed the technique described by Dawson & Olmstead. He found positive agglutination reactions in 59 % of 17 cases of rheumatoid arthritis, and 50 % positive reactions among 10 definite cases of streptococcus infection. There were only 11 % positives in a control material of 152 sera.

In 1946 Cecil & deGara reported finding positive agglutination reactions in 60 % of 268 patients with rheumatoid arthritis. The

Table

Investigators	Year	Antigen	Titre in positive reaction
Cecil, Nicholls & Stainsby	1931	α -Str. «typical»	640
Gay & Gowen	1931	α -Str. «rheumatoid»	640
Dawson, Olmstead & Boots	1932	hemolyt. Str.	160
Keefer, Myers & Oppels	1933	hemolyt. Str. Group A	
McEwen, Chasis & Alexander	1935	hemolyt. Str. Group A	
Dawson, Olmstead & Boots	1936	hemolyt. Str. Group A	160
Goldie	1938	hemolyt. Str. Group A	200
Packalén	1943	hemolyt. Str. Group A	160
Cecil & de Gara	1946	hemolyt. Str. Group A	
Kalbak	1946	hemolyt. Str. Group A	40
Edström & Winblad	1947	hemolyt. Str. Group A	40
Hedlund	1947	hemolyt. Str. Group A	40

number of positives among scarlatina patients was only 25 %, and in a control material there were none, or only very few. In their opinion, the test was more often positive in patients with a severe joint affection, whereas the reaction became weaker and gradually quite negative as the disease improved or was cured.

Kalbak (1946) made use of a slight modification of Dawson & Olmstead's technique and with it obtained 79 % positive reactions among rheumatoid arthritis patients. In the control material the positives represented a very low percentage.

Edström & Winblad (1947) has 76 % positive reactions among 50 patients with rheumatoid arthritis. They claimed that the reaction did not become positive until four or six months after the commencement of the streptococcal infection. Using a somewhat altered technique Thulin (1947) obtained over 90 % positive reactions among patients with rheumatoid arthritis. Hedlund (1947) found 55 % positives among patients of the same kind.

The conclusions to be drawn from these investigations are:

- 1) The agglutination test is best made with hemolytic streptococci of Lancefield's Group A.
- 2) That among polyarthritis patients there are between 50 % and 75 % positive agglutination reactions.
- 3) The percentage of positives in the control materials is very low.

1.

Pts. with rheumatoid arthr.		Control material			
No. of pts.	% + react.	Str. infections		Normals, and other diseases	
		No. of pts.	% + react.	No. of pts.	% + react.
103	94			102	2
	62				
152	69	49	6	207	2
22	55	103	15	176	2
666	51				
28	75				5
17	59	10	50	152	11
268	60		25		2
183	79	147	7	194	2
50	76				
	55				

Own Investigations.

A. Technique.

The technique is based mainly upon that of Dawson & Olmstead, though with certain modifications, whereby the reaction has become rather more specific; the positive percentage among rheumatoid arthritis patients has increased, whereas the control material still gives a very low percentage of positives.

The test is made in the following manner:

A suitable streptococcus is selected, *i. e.* belonging to Group A (though Groups C and G may also be employed). Groups A, C and G are the so-called human-pathogenic hemolytic streptococci, and it is these that form streptolysin. The type is a subordinate matter. The important point is that the bacterium grows diffusely with no tendency to agglutinate spontaneously.

Culture proceeds in a medium which experience shows will give diffuse growth. The composition of the broth is as follows:

To 750 g minced beef add 1.5 litres of mains water. Leave it overnight in the refrigerator (4° C.). Next day, boil the mixture for 15 minutes, then filter through filter-paper, and adjust the pH to 8.0 by adding 5n NaOH. Boil again for 30 minutes. To 500 ml of this meat extract add 5 g peptone (Bacto- or Orthana-peptone) and 2.5 g NaCl. Boil again. Adjust the pH to 8.0 by adding 5n NaOH. Filter into a sterile flask, then autoclave for 20 minutes at 120°. After autoclaving the pH must be about 7.6—7.8.

The broth is thus rather thin without glucose. The small quantity of NaCl is supposed to have a bearing on the diffuse growth of the bacteria. The kind of peptone is very important in getting a successful result. One requirement is that the streptococci grow very slowly out into the broth so that even after about 14 hours growth it is only diffusely turbid. If they grow quickly and strongly, the culture seems to be less suitable as an antigen. Possibly the optimal period of growth varies somewhat for the various strains, but it seems to be more than 10 hours and less than 15.

Having secured a suitable growth, the living culture is used as the antigen and added direct to the serum dilutions. Heat-killed culture can be employed (56° C. for 30 minutes), but this process increases the chances of spontaneous agglutination, so it is better to work with living culture.

The patient serum is diluted with 0.3 % NaCl to 1 : 10—1 : 20 etc. to 1 : 1280, in eight tubes in all. The same amount of living culture is added, so that the final dilutions are 1 : 20—1 : 40 etc. to 1 : 2560. After careful shaking the tubes are left for two hours in a waterbath at 52° for agglutination. They are then left overnight in the refrigerator at 4° and read next day.

Reading is macroscopic. The tubes should be lightly shaken. The culture will have precipitated somewhat as a result of the long period in the refrigerator. If the reaction is negative the sediment shakes up just as diffusely as the original culture. If it is positive the sediment shakes up in clumps consisting of agglutinated streptococci. The strength of the reaction is indicated in four degrees:

4: Large coherent discs which are difficult to shake to pieces. This reaction is very rare. The supernatant fluid is clear. Signified as ++++.

3: The sediment shakes up in coarse clumps. The fluid clear. Signified as +++.

2: The sediment shakes up in medium and small clumps. The fluid clear. Signified as ++.

1: The sediment shakes up in very small «woolly» clumps. The liquid is turbid, signifying that agglutination is only partial. Signified as +.

0: The sediment shakes up diffuse. No agglutination. Signified as 0.

Negative reactions are: All cases where the agglutination in the first tube is 0 or 1, regardless of the degree of agglutination in the next tubes, for instance: 1) 00000000, 2) 11000000 and 3) 01210000.

It is probably most practical in the future to consider an agglutination as 2) as: doubtful positive reaction. In the present work this latter form of reaction is called negative. As strength 2 in the first tube is almost always followed by the weaker strength 1 in the next tube, this means that there will scarcely ever be a positive reaction with a titre of 20 and that therefore the weakest positive reaction will almost always be 1:40. The most frequent positive reaction is for instance 33210000.

B. The Patient Material.

The patient material comprises a total of 1,141 cases, of which 241 are patients with rheumatoid arthritis, and 900 control cases.

1. *Rheumatoid arthritis.*

Table 2.

241 Patients with Rheumatoid Arthritis.

	+ reaction	÷ reaction
168 pts. (various hosp. depts.)	77 %	23 %
73 pts. (own observations)	79 %	21 %

a) 168 serum samples sent to the State Serum Institute by various hospital departments. Of these, 130 gave a positive reaction (77 %) and 38 were negative (23 %).

b) Own observations comprise a positive reaction in 58 cases (79 %) whilst 15 were negative (21 %).

Conclusion: In a material consisting of patients with rheumatoid arthritis there were about 80 % positive agglutination reactions and about 20 % negative.

Especially interesting are the 15 own observations with a negative agglutination test.

Among them are four absolutely certain and typical cases of rheumatoid arthritis in the active phase with elevated sedimentation rate. The fact must therefore be established before going any further that completely typical cases of rheumatoid arthritis occur with a negative agglutination test, clinically indistinguishable from the other cases with positive reaction. To the other negative cases I may add the following comments:

They include two cases of Polyarthritidis psoriatica — the only ones in the material.

Two of the patients have a normal S.R.

In one of the patients the joint pains have just begun and are very slight.

Two have a very old joint affection, 16 and 28 years duration respectively. In both cases it is quite inactive, with complete ankylosis of the joints and otherwise without particular discomfort.

One patient has a normal S.R. and very severe epilepsy. Moreover, she underwent hysterectomy three years ago for severe metrorrhagia. The joint affection began a year later and is not quite typical. There is a very pronounced tendency to contracture and she was operated in both palms for very severe Dupuytren contracture. The joint affection must be described as atypical.

Two other patients have atypical polyarthritis. One mostly resembles scleroderma. The joints have hardly any capsular swelling, but the skin is very tight and the fingers have a tendency to contracture. The other patient may have Arthritis urica, for the serum uric acid is constantly high, and the joint changes are chiefly localized to the principal joints, whereas there are no changes in the fingers.

The cases of rheumatoid arthritis with a positive agglutination test are on the whole of typical character. It would therefore seem justifiable to conclude *that among the polyarthritis cases with a negative agglutination test, there are relatively more of an atypical nature, with a normal sedimentation rate, psoriasis polyarthritis, old and quite inactive cases, or very fresh cases that are just beginning.*

Among the patients with a positive reaction there are four points of particular interest:

1. Is there a connection between the titre and the clinical course?
2. At what stage in the disease does the reaction become positive?
3. At what stage does the reaction become negative again?
4. What effect on the reaction has the treatment (especially gold treatment (Sanocrysin))?

The observations are rather small in number as yet, and therefore the following must be taken with some reserve.

Table 3 shows that most polyarthritis patients have an agglutination titre of 1:80 and 1:160, but that a considerable number reach a value of 1:320 and 1:640.

In the control material the titre of the positive reactions is distinctly lower on an average, 80 % of them being 1:40 and 1:80, and there are none at 1:640.

The evidence thus is, that the strongest reactions occur in patients with rheumatoid arthritis. As far as can be judged, it will probably also be found that patients with the most severe lesions have the highest titre. It is possibly correct when Coburn says, that patients with *Noduli rheumatici* have a particularly high titre, for in my material there are two cases with pronounced and large nodules; for both the agglutination titre was 1 : 640.

Table 3.
Titre Values.

	Agglutination titres					
	1 : 40	1 : 80	1 : 160	1 : 320	1 : 640	
	6	18	19	11	4	
No. of pts. with <i>rheumatoid arthritis</i> and positive agglutination reaction	10 %	31 %	31 %	19 %	9 %	58 pts.
No. of pts. in control material with positive agglutination reaction	13	22	7	2	—	44 pts.
	30 %	50 %	15 %	5 %	—	

We do not know definitely as yet if the reaction can become negative. The probability is that it can, because the test was negative in two old, wholly inactive cases in the third phase; but as we do not know, if the reactions of these patients previously were positive, this is simply a hypothesis; it is scarcely improbable, however. Coburn too claims to have observed that when the joint affection becomes quiescent, the reaction becomes negative.

Another question of particular interest is when the reaction becomes positive. Here again it would be bold to say anything definite. Apparently some considerable time elapses before it happens, and seemingly longer than the two or three weeks it takes for the antistreptolysin reaction to become positive, and in fact for most sero-reactions. Edström & Winblad have reported on some interesting observations suggesting that agglutinin scarcely forms until four to six months after the onset of the disease. This will detract from the diagnostic value of the reaction; but by repeating the test at intervals of about a month there is a chance of observing that a negative reaction becomes positive.

2. *The control material* consisted of 900 people.

1) 64 normals volunteered as blood donors. One had a positive reaction (1.5 %).

2) 130 patients with various medical, ambulant affections, arbitrarily selected from the blood samples sent in for W.R. from the Medical Polyclinic of the Rigshospital.

Only one of these patients had a positive reaction.

3) The Streptococcal Infection Group consisted of infections with hemolytic and non-hemolytic streptococci.

There were 20 patients with scarlatina in the third—fourth week of the attack. None of them gave a positive reaction. Next, 38 sera were selected with an especially high antistreptolysin-titre (≥ 800). None of these gave a positive reaction either. But among 100 sera from rheumatic fever patients there were 10 % with a positive reaction.

Actually, the only definite infection with non-hemolytic streptococci is the sub-acute bacterial endocarditis (*Endocarditis lenta*). Nine cases, all verified by repeated positive blood cultures with finds of *Str. viridans* in each case, gave a negative agglutination reaction. This strengthens the supposition, that the reaction is specific to hemolytic *Str.* If the reaction were positive in the case of streptococcal infections in general, we should certainly expect it to be positive in a disease like *Endocarditis lenta*, in which there is bacteriemia and the streptococci occur freely in the blood stream.

Table 4.
900 Control Patients.

Diagnosis	No. of pts.	Positive aggl. reaction	Negative aggl. reaction
Normal (donors)	64	1.5 %	98.5 %
Medical affections (ambul.)	130	0.8 %	99.2 %
Scarlatina	20	0	100 %
Sera with A.S.T. ≥ 800	18	0	100 %
Rheumatic fever	100	10 %	90 %
Endocarditis lenta	9	0	100 %
Arthritis gonorrhoea	18	0	100 %
Various «rheumatic» affections	41	15 %	85 %
Medical affect. (hosp. pts.)	500	7 %	93 %

4) As examples of other infectious joint affections I have included 18 cases of Polyarthritis gonorrhoeica. None of the blood samples reacted positively.

5) A group of patients with »various rheumatic affections» but excluding rheumatoid arthritis consisted of 41 from the Department of Rheumatology and Physical Medicine of the Kommunehospital, comprising patients with arthrosis, rheumatic fever, sciatica, poliomyelitis seq. etc. In this group the reaction was positive in 15 %.

Thus it is among rheumatic fever patients and in this latter group that we find the highest agglutination percentage in the control material. As the last-named group includes rheumatic fever patients, this is presumably the explanation of the relatively high percentage of positive reactions.

6) Finally, there is a group of hospitalized patients suffering from various medical affections, all in the Nørre Hospital. A total of 533 patients were systematically tested with this reaction. Of these, 33 had chronic polyarthritis, and these were accounted for when dealing with this group of patients.

Of the remaining 500, a positive agglutination reaction was obtained from 36, or 7 %.

The diagnoses in this patient material cover a wide variety of medical diseases, but among the patients with a positive reaction one kind of diseases is particularly represented: chronic inflammation in the respiratory tract. Of the 36 patients, 14 had chronic infections of this kind (chronic bronchitis, sometimes combined with asthma, unspecific lung infiltration, bronchiectasiae, chronic sinusitis, chronic tonsillitis etc.). In addition, there are 5 cases of cardiac insufficiency with lung stasis. The remaining 17 cases represent various diagnoses.

Discussion.

The importance of the reaction may be appraised in the following two ways:

- I) The immediate diagnostical value,
- II) Its importance for the elucidation of the etiology of rheumatoid arthritis.

I) As it appears now from this and previous works, it may be considered established that the reaction is positive in the majority of patients with rheumatoid arthritis, while negative in the majority of other diseases. Already in this fact may be found a certain diagnostical value. But as the reaction is not »absolute» (*i. e.* positive in all cases of rheumatoid arthritis and negative in all

other diseases), its diagnostical value is as yet rather limited, and critical judgment should accompany its use. It may be a mere technical problem to make the reaction more »specific« for rheumatoid arthritis and continued research may possibly solve this problem.

II) However, the importance of the reaction for the elucidation of the etiology of rheumatoid arthritis is of special interest. The deciding factor is to establish whether the reaction is a specific expression of an infection with hemolytic streptococci or not. It may be difficult to establish definite proof and much seems to indicate that in many ways this sero-reaction acts differently and in an unexplained manner from other sero-reactions.

That rheumatoid arthritis should be an ordinary infectious disease caused by streptococci is contradicted by the following facts:

- 1) So far it has never been possible to cultivate hemolytic streptococci from synovia, blood or lymphatic glands of patients with rheumatoid arthritis,
- 2) penicillin seems to be quite inactive in rheumatoid arthritis,
- 3) the apparent disconformity between the antistreptolysin reaction and the agglutinin reaction.

If we examine the A.S.T. in a large material consisting of patients with rheumatoid arthritis we find that its distribution is exactly the same as in a normal material (Kalbak 1944, 1946), that is to say, we find only about 10 % of increased values. Thus the antistreptolysin reaction alone provides no basis for attributing the infection of these patients to hemolytic Str.

Then how shall we explain that hemolytic streptococci agglutinate in the serum of about 80 % of these patients? Surely both reactions are an expression of an infection by these bacteria? Should not both reactions be positive if there were really an infection by streptococci?

This argument is only apparently right. Both reactions are an expression of an infection with hemolytic streptococci, it is true, but each represents two different mechanisms of immunity. The one (the antistreptolysin reaction) is an *antitoxic* reaction, the other (the agglutination reaction), on the other hand, is an *anti-bacterial* reaction.

This means that first and foremost the antistreptolysin reaction is a reflection of the function of the streptococci, their toxin formation in the organism, whereas the agglutination reaction

merely expresses the presence of the bacterium itself, dead or living.

Thus the antistreptolysin reaction depends upon two factors: 1) The presence of hemolytic streptococci, and 2) that these streptococci are living and capable of producing toxin (streptolysin). The agglutination reaction depends only on there being hemolytic streptococci in the organism — it seems immaterial whether they are living and highly virulent; greatly attenuated or even dead.

Thus we may quite well imagine the possibility that the streptococci become attenuated so much that their production of toxin ceases and the antistreptolysin reaction becomes negative, whilst the agglutinins are still being produced and cause a positive agglutination reaction. If we compare this with Edström & Winblad's observation that the formation of agglutinin only becomes perceptible after the disease has lasted four to six months, this will explain the apparent contradictions. Theoretically there is actually no contradiction when the antistreptolysin reaction is negative and the agglutination reaction positive.

Even if theoretically there is no reason why the two reactions may not diverge and still be an expression of an infection by streptococci, it is still with some apprehension that one transfers this interpretation to actuality, because the disease may consequently be considered a chronic bacteriemia with hemolytic streptococci, which is not in accordance with the observations made so far.

In his works from 1946 and 1947 Wallis makes himself the spokesman of the reaction being unspecific. He explains the agglutination as a consequence of the peculiar tendency of these sera to react with the antibodies normally present against various bacteria, *f. inst.* hemolytic streptococci. Even if this explanation is far from satisfactory, the examinations are so consistent that the results give cause for meditation, and it is without doubt that the conception of the agglutination reaction as a specific streptococcus reaction has been countered on very important points.

The conclusion is that the problem whether the reaction is specific or not is far from being solved. If one is to appraise the present position, most circumstances seem to indicate that it is an unspecific serological reaction, the nature of which is quite unknown. Further knowledge will undoubtedly throw a new light

over the etiological problems connected with rheumatoid arthritis and there is, therefore, all possible reason to continue the systematical studies of the real nature of this reaction.

Summary.

The author refers to earlier investigations of the agglutination test with streptococci. His own technique is described. Among 241 rheumatoid arthritis patients the agglutination test was positive in about 80 %. Among 900 control patients it was positive in only a very low percentage of cases.

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On Number and Arrangement of Nuclear Lobes of Neutrophils in Diseases of the Liver.

By

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(Submitted for publication September 11, 1947.)

Introduction.

A strong increase in the number of lobes of the neutrophil leucocytes is, as known, typical of pernicious anemia. This symptom is observed, although in a lesser degree, also in sprue, beriberi, and scurvy, and in the aged (Åberg and Tötterman). In the majority of these conditions an enlargement of the erythrocytes occurs simultaneously. The increase in size is greatest in pernicious anemia but also distinctly denoted in the aged (Hernberg). In liver diseases, both chronic and acute, a number of workers have often stated macrocytosis (C. Gram, Jørgensen and Warburg, Mogensen, Schulten and Malamos, Wintrobe, and others). Greta Hammarsten and co-workers have made a thorough study of this phenomenon in epidemic hepatitis. They found it exceedingly constant and attach great diagnostic and prognostic value to this symptom. The white blood picture in diseases of the liver has not, on the other hand, aroused much interest. Fellingner and Klima certainly observed leucopenia in cirrhosis and Masina, in addition, a slight neutropenia and lymphocytosis. The last-mentioned author stresses, however, that a coarse pathological granulation of the monocytes, observed by Naegeli, is a very characteristic change in cirrhosis. According to Naegeli and Bloor the neutrophil leucocytes and the lymphocytes show no divergences, excepting possibly a slight vacuolization of the neutrophil leucocytes. As

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macrocytosis and poly-lobation of the neutrophils occur very frequently simultaneously, as mentioned, and as the macrocytosis seems to give valuable information regarding the course of the acute hepatitis, an investigation of the nuclear lobes in jaundice seemed called for.

Series and Results.

The series comprises 40 cases of jaundice or undoubted diseases of the liver from the Second and Third Medical Clinics. The majority of the patients were examined several times during the course of the disease. Besides calculating the lobar mean in 100 leucocytes the mean diameter of the red cells was determined with Bock's erythrocytometer in each case. By this method a fairly reliable approximate value is obtained (S. Björk, G. Hammarsten, and others) which is considered sufficient in this connection. The degree of jaundice was given according to Meulengracht's icterus index, and the urine (in the majority of cases) was examined as to bile pigment with iodine, Ehrlich's, and Schlesinger's tests, regarding bilirubin, urobilinogen, and urobilin respectively. The Takata-Ara and thymol liver function tests were often carried out and occasionally a prothrombin index was determined according to Quick and Lehmann. A complete blood picture of the majority of the patients was made.

For the purpose of obtaining a clear survey of the results the cases of the different liver diseases were subdivided into groups. The largest group, 25 cases, comprised acute hepatitis; in 5 cases cirrhosis was diagnosed and in 5 carcinomatosis hepatis. In 3 cases there was chronic hepatitis and in 2 cholelithiasis. For the purpose of control the same laboratory assistant determined the number of lobes of 5 healthy males and of 5 females, and, furthermore, for comparison, of 10 cases of pernicious anemia.

In the healthy persons the mean of the number of lobes was 3.0, more closely 2.98, which is somewhat higher than Arneth's value 2.9 and Cook's, and Åberg and Tötterman's which was 2.7. It is of importance that every worker should have a control series of his own as the subjective determination plays a certain part, if not an important one. The distribution of the lobes agreed with observations made by other investigators. Nuclei with 3 lobes were decidedly in the majority, 4 lobes were infrequent, and 5 lobes rare. The halometric mean diameter of the erythrocytes was 7.1, the lowest value 6.9 and the highest 7.3. As expected the

lobar mean and the average erythrocyte diameter in the series with pernicious anemia was greatly increased, being 3.8 and 7.9 respectively.

Studying lobar conditions in acute hepatitis, values, higher than those found in healthy persons, were often observed. Values amounting to 3.5 and 3.6 were not infrequent; once a value of 4.4 was noted, and twice 3.9. The rise was due to an increase in the number of leucocytes with 4 lobes and to a small degree to such with 5 lobes. Even 6 lobes were occasionally observed. Distinct, definite variations appeared clearly in the majority of the examined cases several times. The highest lobation values in the isolated cases generally appeared three to six weeks after the onset of the disease. They decreased again and returned to the normal about two months after sickening.

In the cases of cirrhosis no definite increase in the number of lobes was stated in 3 patients (26, 27, 28). These were all of the atrophic type without mentionable jaundice. In the two remaining cases (29, 30) the number of lobes was somewhat increased; simultaneously there was an abundance of bile pigment in the blood and urine. In the four definite cases of carcinomatosis hepatitis there was no poly-lobation, however, despite fairly severe icterus. In the fifth case, in which the diagnosis wavered between tumour and hepatitis and the sudden onset of the disease with a high temperature spoke in favour of the latter diagnosis, the number of lobes increased slowly (within $3\frac{1}{2}$ week). The patient died; a post-mortem examination, which was not permitted, however, would have been of great interest.

One of the three cases of chronic hepatitis (36) showed a strong poly-lobation. There was an acute exacerbation at the time, earlier the course of the disease had periodically proceeded without particularly marked symptoms. One of the two remaining cases (37) showed a slight increase in the number of lobes, the third case (38) a normal value which may perhaps have been due to a complication; the uncommonly severe leucocytosis supports this assumption. One of the two cases with cholelithiasis (39) was a fairly fresh case in comparison with the second one (40). The former case, admitted one month after sickening, showed an increase in the number of lobes. This value rose again one week later and sank during the following week. In the latter case in which the disease had started about three months earlier, there was no poly-lobation during the period of three months in hospital.

10	49 f.	Hepatitis. acut. Lucas sero neg.	2.5.47	3.6.47 12.6.47 19.6.47 25.6.47	6,200 4,900 4,200 4,300	3.1 3.3 3.4 3.2	2-3-1-(5) 2-3-4-(5) 2-3-1-(5) 2-3-4-(5)	7.5 7.8 7.6 7.4	1:50 1:45 1:23 1:12	+	+
11	43 f.	Hepatitis. acut.	27.5.47	3.6.47 10.6.47 19.6.47 26.6.47 19.6.47 27.6.47 11.7.47 18.7.47 25.7.47 21.6.47 28.6.47 12.7.47 19.7.47 20.6.47 27.6.47	4,600 4,800 4,100 3,800 4,600 4,500 3,400 4,600 4,000 3,200 4,300 4,200 5,100 2,800 2,700	3.0 3.1 3.3 3.2 3.2 3.2 3.4 3.1 3.1 3.1 3.2 3.6 3.4 3.5 3.3	2-3-1-(5-6) 2-3-4-(5) 2-3-4-(5-6) 2-3-4-(5) 2-3-1-(5-6) 2-3-4-(5) 2-3-1-5 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) (2)-3-4-(5-6) 2-3-1-(5) 2-3-4-5 2-3-1-(5-6)	7.5 7.6 7.7 7.5 7.6 7.6 7.5 7.2 7.2 7.9 7.6 7.8 7.3 7.3 7.7	1:16 1:45 1:80 1:20 1:25 1:120 1:35 1:24 1:18 1:125 1:40 1:25 1:16 1:18 1:8	+	+
12	45 f.	"	27.5.47	3.6.47 10.6.47 19.6.47 26.6.47 19.6.47 27.6.47 11.7.47 18.7.47 25.7.47 21.6.47 28.6.47 12.7.47 19.7.47 20.6.47 27.6.47	4,600 4,800 4,100 3,800 4,600 4,500 3,400 4,600 4,000 3,200 4,300 4,200 5,100 2,800 2,700	3.0 3.1 3.3 3.2 3.2 3.2 3.4 3.1 3.1 3.1 3.2 3.6 3.4 3.5 3.3	2-3-1-(5-6) 2-3-4-(5) 2-3-4-(5-6) 2-3-4-(5) 2-3-1-(5-6) 2-3-4-(5) 2-3-1-5 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) (2)-3-4-(5-6) 2-3-1-(5) 2-3-4-5 2-3-1-(5-6)	7.5 7.6 7.7 7.5 7.6 7.6 7.5 7.2 7.2 7.9 7.6 7.8 7.3 7.3 7.7	1:16 1:45 1:80 1:20 1:25 1:120 1:35 1:24 1:18 1:125 1:40 1:25 1:16 1:18 1:8	+	+
13	30 f.	"	1.6.47	3.6.47 10.6.47 19.6.47 26.6.47 19.6.47 27.6.47 11.7.47 18.7.47 25.7.47 21.6.47 28.6.47 12.7.47 19.7.47 20.6.47 27.6.47	4,600 4,800 4,100 3,800 4,600 4,500 3,400 4,600 4,000 3,200 4,300 4,200 5,100 2,800 2,700	3.0 3.1 3.3 3.2 3.2 3.2 3.4 3.1 3.1 3.1 3.2 3.6 3.4 3.5 3.3	2-3-1-(5-6) 2-3-4-(5) 2-3-4-(5-6) 2-3-4-(5) 2-3-1-(5-6) 2-3-4-(5) 2-3-1-5 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) (2)-3-4-(5-6) 2-3-1-(5) 2-3-4-5 2-3-1-(5-6)	7.5 7.6 7.7 7.5 7.6 7.6 7.5 7.2 7.2 7.9 7.6 7.8 7.3 7.3 7.7	1:16 1:45 1:80 1:20 1:25 1:120 1:35 1:24 1:18 1:125 1:40 1:25 1:16 1:18 1:8	+	+
14	40 f.	"	4.6.47	3.6.47 10.6.47 19.6.47 26.6.47 19.6.47 27.6.47 11.7.47 18.7.47 25.7.47 21.6.47 28.6.47 12.7.47 19.7.47 20.6.47 27.6.47	4,600 4,800 4,100 3,800 4,600 4,500 3,400 4,600 4,000 3,200 4,300 4,200 5,100 2,800 2,700	3.0 3.1 3.3 3.2 3.2 3.2 3.4 3.1 3.1 3.1 3.2 3.6 3.4 3.5 3.3	2-3-1-(5-6) 2-3-4-(5) 2-3-4-(5-6) 2-3-4-(5) 2-3-1-(5-6) 2-3-4-(5) 2-3-1-5 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) 2-3-4-(5) (2)-3-4-(5-6) 2-3-1-(5) 2-3-4-5 2-3-1-(5-6)	7.5 7.6 7.7 7.5 7.6 7.6 7.5 7.2 7.2 7.9 7.6 7.8 7.3 7.3 7.7	1:16 1:45 1:80 1:20 1:25 1:120 1:35 1:24 1:18 1:125 1:40 1:25 1:16 1:18 1:8	+	+
15	24 f.	" recid.	15.7.47 (15.5.47)	12.8.47 20.8.47 21.8.47	4,500 4,100 3,100	3.1 2.9 2.9	2-3-1-(5) 2-3-4-(5) 2-3-4	7.7 7.6 7.6	1:120 1:110 1:50	+	+
16	23 f.	Hepatitis. acut.	10.5.47	23.5.47	3,100	3.2	2-3-1-(5)	7.2	1:16	+	+
17	50 f.	"	28.5.47	12.6.47	2,800	2.8	2-3-4-(5)	8.0	1:45	+	+
18	64 f.	"	5.5.47	28.5.47	3,500	3.4	2-3-1-(5-6)	7.6	1:12	+	+
19	26 f.	"	15.7.47	4.6.47 25.7.47 15.8.47	4,400 4,000	3.9 2.9 3.2	2-3-4-5(6) 2-3-4-(5) 2-3-4-(5)	7.9 7.6 7.6	1:10 1:60 1:10	+	+
20	31 f.	"	28.6.47	21.8.47 28.7.47 7.8.47	5,100 5,900 3,200	3.2 3.2 3.2	2-3-4-(5) 2-3-4-(5) 2-3-4-(5)	7.7 7.6 7.6	1:10 1:70 1:45	+	+

Table 1 (cont.).

Pat.	Age sex	Diagnosis	Date of onset	Date of examination	White cell count	Lobation mean value	Arrangements of lobes	Mean diam. of erythr.	Icterus index	Urine: I. E. Schl.	Takata	Thymol
21	35 f.	Hepatit. acut.	10. 6. 47	18. 7. 47	2,300	3.0	2-3-4-(5)	7.2	1:140	+-	+	
22	45 f.	"	5. 7. 47	21. 8. 47		2.7	2-3-4	7.0	1:15	--		
23	15 f.	"	22. 4. 47	28. 7. 47	3,100	3.4	2-3-4-(5)	8.0	1:30	++	+	
24	23 f.	"	5. 5. 47	29. 4. 47		2.8	2-3-4	7.3	1:60	++	+	
25	42 m.	"	10. 3. 47	8. 5. 47	5,800	3.1	2-3-4-(5)	7.3	1:10	--	+	
26	58 f.	Cirrhosis hepatitis atrophica	15. 2. 47	21. 5. 47	11,500	3.3	2-3-4-(5)	7.4	1:120	++	+	
				28. 3. 47		3.0	2-3-4	7.2	1:50	--		
27	35 f.	Cirrhosis hepatitis atrophica Lucs sero pos. me- die.	15. 2. 47	29. 3. 47	6,300	2.7	2-3-4	7.5	1:3	+-	++	+
				12. 7. 47	4,500	2.9	2-3-4	7.2	1:8		+	+
				26. 7. 47		2.9	2-3-4	7.1				
				9. 8. 47		3.2	2-3-4					
				21. 6. 47	3,000	3.2	2-3-4-(5)	7.3	1:16	+-	+	+
			20. 12. 47	12. 7. 47	8,000	2.8	2-3-4	7.1	1:7			+
				2. 8. 47		2.7	2-3-4	7.3	1:29			+
				18. 8. 47		3.0	2-3-4	7.2				
28	43 f.	Cirrhosis hepatitis	16. 6. 47	15. 7. 47	4,200	2.8	2-3-4-5	7.4	1:17	--	-	
29	52 f.	Atrophin hepatitis subac.	1. 1. 47	9. 5. 47	12,900	3.4	2-3-4-(5)	7.6	1:75	++	+	
30	61 m.	Cirrhosis hepatitis	15. 11. 47	8. 5. 47	4,550	3.4	2-3-4-5	7.3	1:100	++	+	

Comment.

This investigation shows that a passing »shift to the right», according to Arneth's classification, seems to occur fairly regularly during the course of acute hepatitis. A poly-lobation was also observed in chronic hepatitis and in cirrhosis combined with distinct jaundice. This was also the case in a patient with fairly fresh cholelithiasis, while there was no poly-lobation, on the other hand, in a second patient who had suffered from the disease for some length of time before being examined, and in 4 cases of carcinomatosis hepatis, all of these combined with severe icterus.

Before attempting to describe the possible arise of poly-lobation in diseases of the liver there is reason to give a brief account of the common conception of this pathological phenomenon. It has namely frequently been shown, and is generally admitted, that the Arneth count in healthy human beings is remarkably constant. Naegeli's opinion, based on Brugsch and Schilling, is, that the origination of the lobes is the result of a normal process of ripening connected with the motility of the cells, which is a conception he shares with other workers. He stands alone, however, regarding the opinion of the extremely increased lobation, in, for instance, pernicious anemia, being due to a strong reactive activity of the bone-marrow. Ponder stresses that time is the primary factor in the development of neutrophil leucocytes into forms with a greater number of lobes. Bond, and Crosman and Charipper show in their investigations that an increased activity of the cells furthermore acts greatly in this direction. According to Bond neutropenia, accompanied by activity in the small number of cells, in combination with a reduced liberation from the bone-marrow may be the cause of poly-lobation in pernicious anemia. — Acute hepatitis is characterized, as is a number of other diseases caused by virus, by leucopenia which might, at least partly, be the cause of the origination of a shift to the right of the leucocytes. This is not the sole reason, and evidence to this effect is found in that there are cases (29, 35) with leucocytosis and distinctly increased lobation, and the opposite, a great number of cases with a very low white cell count and no poly-lobation. This agrees with Ponder's results based on his experience and theoretical considerations. He says: »The number of cells in the various Arneth classes is in no way dependent on the number of cells in the blood-stream, for the only essential is that the number of cells

entering the circulation is equal to the number leaving — a condition compatible with a leucocytosis, a leucopenia, or with a normal polymorph count.»

Is the degree of jaundice the decisive factor in the origination of poly-lobation in diseases of the liver? A similar question has been made earlier by investigators of macrocytosis in jaundice. C. Gram and Meulengraecht were of the opinion that there was a direct relation between the enlargement of the erythrocytes and the degree of jaundice while Jørgensen and Warburg did not state a parallelism of this kind. This was also the case regarding the correlation between lobation and icterus if conclusions are drawn from the results obtained in the series of this investigation. There was, as already mentioned, a high-grade icterus with normal Arneth count in carcinoma and cholelithiasis, and in acute hepatitis the increase in Arneth's count does not seem to proceed parallel to the variations in the icterus index. In cirrhosis and chronic hepatitis it seems, however, judging from the material at my disposal, that an increased jaundice predisposes an increase of poly-lobation. Is this due to the jaundice, in this case, being an expression of a temporarily greater activity in the pathological processes in the liver or to the jaundice adding to another factor, still unknown?

According to this investigation series there is no parallelism between lobation and macrocytosis. The changes in the size of the erythrocytes in the patients examined several times show, as does poly-lobation, a certain regularity in the majority of cases, although the two curves are not parallel as a rule. Whether the macrocytosis is the result of a pathological regeneration or due to changes in the blood influencing the size of the erythrocytes is a theoretic question of interest put by Mogensen but which, so far, has not been finally solved. Certain factors speak, however, for the former assumption being correct; Greta Hammarsten found, for instance, in a case of acute hepatitis at the recovery, a long interval between the normal diameter of fresh formed red cells and the older enlarged ones. Also the changes in lobation support the theory of a bone-marrow affection causing the shift to the right. The centrally caused leucopenia would, with »time ageing» and increased activity of the leucocytes lead to poly-lobation. There may, again, be a relation between the causative factor of the disease (virus), endogen toxins produced by the chronic liver inflammations, or, the retained bile pigments which

may all be considered to have a checking influence on the hemato-poiesis. Due to the fact that several factors may be active no definite correlation between poly-lobation or macrocytosis and one single factor as for instance the degree of jaundice is obtained. Poly-lobation in the present series seems to be more of a passing nature than is the macrocytosis. This explains why Gloor and Naegeli did not find changes in the leucocytes in cirrhosis of the liver. A determination of Arneth's count in diseases of the liver is not, perhaps, of the same value in making the prognosis as may possibly be the macrocytosis. The shift to the right would inform us of whether the process causing jaundice is in an acute stage or not.

Summary.

1. In acute hepatitis a passing shift to the right of Arneth's count appeared frequently. It was greatest three to six weeks after the onset of the disease and abated later.

2. A poly-lobation was observed in chronic hepatitis, cirrhosis, and cholelithiasis when combined with jaundice but, on the other hand, in no case of atrophic cirrhosis of the liver, carcinomatosis hepatis, and cholelithiasis, all in an advanced stage.

3. There was no correlation between the shift to the right and the degree of jaundice or a pathological change in such liver function tests as Takata-Ara, thymol, and prothrombin index. The course of the poly-lobation was not parallel to the macrocytosis which seemed to be more constant in chronic diseases of the liver than was the poly-lobation. On that account the macrocytosis is of greater importance in making the prognosis.

4. Poly-lobation in diseases of the liver is probably due to checking of the hematopoiesis followed by leucopenia and increased activity and ripening of the fairly small number of leucocytes in the blood. Injectable liver preparations have no effect on the phenomenon.

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The Influence of Diet on the Renal Function of Healthy Persons.

By

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Although the urea clearance test is one that has obtained wide use in the clinic since the appearance of Møller, McIntosh & Van Slyke's work in 1928, publications on the influence of diet on the urea clearance are few, while still fewer are investigations into the influence of diet on the renal function as elucidated by inulin clearance and diodrast clearance.

As long ago as in 1923 Addis & Drury reported that a few hours after the persons tested had ingested milk, coffee or glutamic acid, the urea clearance rose, whereas cane sugar and whiskey had not that effect. Since then the urea clearance is determined on *fasting* persons or at any rate after a morning meal poor in protein and free of coffee.

In 1931 Jolliffe & Smith, later Shannon, Jolliffe & Smith (1932), Van Slyke, Rhoads, Hiller & Alving (1934) and others showed that in dogs the urea clearance varies very considerably with the protein metabolism. A meat meal will result in a rather brief but marked increase in the urea clearance, whereas the lowest values are only reached after several days on a protein-poor diet or fasting. Herrin, Rabin & Feinstein (1937) in the case of dogs demonstrated that glycine, d-, l-alanine and glycolic acid like meat, after some days on a protein-poor diet, cause a strong increase in the urea clearance. The same applied to N-free sub-

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stances such as lactic acid, pyruvic acid, acetic acid, propionic acid, whereas gluconic acid, which is not broken down by tissue in vitro, had no effect.

In man after a low protein diet Cope (1933), Goldring et al. (1934) and Longley & Miller (1942) were able to demonstrate a drop in the urea clearance such as that observed in the dog. On passing from an ordinary diet to a diet poor in protein the fall was about 30 %. Cope observed a similar fall in nephritics, though it was less pronounced.

Whereas the fall in the urea clearance on a diet poor in protein is well established, there are fewer works on the effect on ultrafiltration and the blood flow through the kidneys.

In the dog Jolliffe & Smith (1931) proved that with diureses over the augmentation limit the urea clearance rose and fell exactly parallel with the creatinine clearance, the urea-clearance: creatinine clearance ratio being very constant. As the creatinine clearance in the dog is regarded as an indication of the value of the ultrafiltration, it is possible without much error to estimate the ultrafiltration from the urea clearance when the diuresis is high.

Smith et al. (1938) state that in man the ratio urea clearance: inulin clearance on an ordinary diet is fairly constant, varying from 0.51 to 0.67 and averaging about 0.57. In 1940 Smith stated that in man, or at any rate in adults, the ultrafiltration is relatively insensitive to dietary changes; this observation differs from conditions in the dog, where the fluctuations of the urea clearance and the ultrafiltration ran parallel.

On the blood flow through the kidneys there is a work by Van Slyke, Rhoads, Hiller & Alving (1934) dealing with conditions in the dog. These authors, employing a special method on a dog with explanted kidney, were able, by simultaneous sampling from *arteria* and *vena renalis*, to determine the urea content in the blood before and after passage through the kidney, and to calculate the blood flow by dividing the difference into the quantity of urea excreted per time unit. They found approximate parallelity between urea clearance and blood flow on a diet with a varying N-content. Pitt (1944) tested the ultrafiltration and blood flow of dogs by means of the creatinine clearance and the para-aminohippuric acid clearance under variations in the protein content of the diet and when glycine was infused intravenously. Small amounts of glycine and an increase in the protein content

of the food gave the same result, *i. e.* an increase of blood flow and ultrafiltration, but a reduced filtration fraction.

So far, nothing is known regarding the renal blood flow in man when the supply of protein is reduced (Smith 1940).

Own Experiments.

The *individuals* employed in the tests were 8 women aged from 18 to 40 years with healthy kidneys. Three of them were suffering from protrusion of the intervertebral disk, the others were quite healthy, going about and working as nurses.

The *diet* consisted either of ordinary diet, perhaps supplemented with 100 g of meat daily, or of food poor in protein, a modified Holten's diet with an average daily protein content of 26.7 g (24.4—29.1), corresponding to 4.27 g N (3.91—4.66). The ordinary diet was adequate in calories, whereas the diet poor in N with its 2,000 calories generally involved a loss of weight in the individuals who were up, whilst those in bed maintained their weight. The persons received the N-poor diet for an average of 13.1 (9—18) days before the test, and the N-rich diet correspondingly at least 8 days, usually for some weeks. With four of the persons the test was repeated with similar results. Daily determinations of the N-excretion in the urine were made for control purposes on all those who were up.

The *clearance tests* were made fasting, though in one or two cases after a light morning meal. All the tests were made with the catheter *à demeure* as well as bladder lavage with 50 ml water and a little air. Inulin and diodrast were infused continuously intravenously after a priming infusion. Fluids being given in ample amounts, diuresis was well under way before the test began and was maintained at such a level that the maximum clearance could always be calculated. As a rule three clearance periods of about 15 minutes each were used, the first period at the earliest about 30 minutes after the commencement of the intravenous infusion. The clearance values found were corrected to a body surface of 1.73 sq.m.

Technique of analysis. The urea was determined by Van Slyke's urease method, urine-nitrogen by micro-Kjeldahl, inulin by the diphenylamine method, diodrast by Bak, Brun & Raaschou's modification (1943) of White & Rolf's method (1940).

Results. On 8 persons we made a total of 28 series of determinations of the urea, inulin and diodrast clearances, partly after a normal diet, partly after a diet poor in protein. For three days prior to the tests the nitrogen excreted in the 24-hours' urine on a normal diet averaged 13.54 g (8.0—18.2), on N-poor diet 4.32 g (3.1—5.48). On normal diet the diureses averaged 1 070 ml (655—1 473), on low protein diet 699 ml (422—1 081). Whereas the blood urea on the normal diet was 25.6 mg per 100 ml (18.5—39.8), on the low protein diet it fell to 15.5 mg per ml (12—21). The results as a whole will be seen from Table 1.

The first column shows the ratio between the inulin content of the urine and of the plasma (In U/P), in other words the concentration index. This is everywhere so low that the values are far beyond the «augmentation limit», and moreover so uniform on the two forms of diet that variations in the concentration index can have no bearing on differences in the urea clearance. The next columns show the inulin clearance, blood urea, urea clearance and diodrast clearance. The variations in the blood urea have already been commented upon. The three clearance values are all corrected to a body surface of 1.73 sq.m. A comparison between the two groups shows that on the ordinary diet the urea clearance averages 75.6 ml per minute, on the low protein diet 50.4 ml per minute, which gives a fall of 33 %. The corresponding values for inulin clearance are 130.1 and 121.5 (\div about 7 %), for diodrast 626 and 612 ml per minute (\div about 2 %). These average values are calculated from the means of every series of determinations.

Discussion. It will be seen that a diet poor in protein involves various changes in the renal function. Together with the fall in the N-excretion there is a fall of the diuresis, a phenomenon with which we are familiar from Folin's work on the subject (1917). Further, we see regularly a fall of the blood urea, but not at all directly proportionate to the N-excretion, as we were unable to force the blood urea below 12 mg per 100 ml. This is explained chiefly by the circumstance that in the great majority of cases there is a considerable drop in the urea clearance on the low protein diet; the lower diuresis will have an effect in the same direction, though this is not entirely certain, as it is probable that the «augmentation limit» is also displaced downwards on a diet poor in protein. Whereas the fall in the urea clearance is considerable and fairly certain statistically ($t = 1.73$), the difference

Table 1.

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Table 1.

Normal Diet						Low Protein Diet					
Name & Date	In. U/P	In. cl. (ml)	Urea in blood mg p. 100 ml	U. cl. (ml)	Diod. cl. (ml)	Date	In. U/P	In. cl. (ml)	Urea in blood mg p. 100 ml	U. cl. (ml)	Diod. cl. (ml)
J. J. 23-1	9.6 9.0 10.0	106.0 113.7 108.0	29.0 28.0 27.5	92.4 94.5 84.8	510 479 422	5-2	11.9 17.8 14.6	113.7 112.9 131.7	15.5 15.0 15.0	53.3 52.5 68.4	482 471 508
H. J. 2-10	5.9	104.0	21.0	82.0	593	18-10	12.5 8.5	115.5 97.0	12.5 11.5	48.7 46.9	655 512
V. J. 11-11	7.0 8.6	129.8 109.8	24.5 25.2	73.8 54.4	692 649	1-12	4.5 4.8	102.6 94.6	13.8 14.5	66.5 70.6	836 728
17-1	9.2 9.0 12.5	165.8 172.7 122.9	28.8 28.9 29.0	95.0 82.2 76.3	673 613 548	29-1	8.5 10.8 9.3	117.2 112.9 136.8	21.2 20.0 19.1	53.2 61.2 48.4	645 605 719
E. L. 17-2	12.9 8.8 12.9	173.0 127.0 124.9	19.0 18.5 18.0	103.8 96.4 83.8	1080 872 686	5-3	10.5 10.6 10.7	122.5 140.0 132.1	13.5 13.0 12.5	44.8 38.9 43.5	778 839 774
E. N. 11-11	7.8 5.9	128.5 120.3	24.0 23.5	84.4 87.9	988 795	27-11	12.1 12.2	144.4 136.2	15.0 15.0	41.9 38.2	635 586
A. S. 8-11	6.2 9.3	121.4 108.2	26.0 26.0	65.0 46.0	695 534	27-11	7.1 7.6	101.3 106.2	18.4 16.8	25.5 38.2	638 616
14-1	12.0 8.6 8.6	176.5 158.3 137.7	39.2 39.8 40.0	66.4 76.1 65.1	647 615 532	26-1	10.2 10.0 12.1	178.5 152.3 143.9	21.0 21.0 21.0	60.0 59.1 59.1	774 558 607
H. S. 17-1	9.9 15.7 17.6	146.9 124.6 144.3	31.0 32.0 34.0	53.4 49.1 52.9	652 577 731	14-2	9.3 8.8 10.6	115.4 110.1 104.6	14.0 13.0 12.0	70.6 67.2 64.1	624 587 534
31-1	16.3 13.0 11.1	124.5 135.8 152.6	27.8 28.5 28.5	61.2 82.1 71.8	627 760 696	26-1	9.8 9.3 8.8	132.0 132.2 122.2	15.5 15.1 14.5	43.6 45.4 43.8	571 606 607
23-2	9.4 9.6	145.8 146.3	25.0 24.5	72.5 70.5	622 591	26-1	9.8 9.3 8.8	132.0 132.2 122.2	15.5 15.1 14.5	43.6 45.4 43.8	571 606 607
11-1	9.7 14.4	135.7 116.5	26.0 26.0	89.6 73.4	695 555	26-1	9.8 9.3 8.8	132.0 132.2 122.2	15.5 15.1 14.5	43.6 45.4 43.8	571 606 607
A. V. 17-1	8.4 6.5 6.8	109.1 119.1 120.7	19.0 19.0 18.0	66.4 62.1 73.2	482 537 536	14-2	8.2 8.1 8.0	129.1 128.2 110.0	16.5 16.0 16.0	38.3 31.1 46.7	531 569 478
31-1	7.9 7.7 9.4	138.6 122.5 122.6	24.0 24.0 24.0	86.7 81.5 76.4	608 517 468	26-1	9.3 9.2 9.1	112.2 108.9 127.1	14.3 14.2 14.1	40.4 38.2 45.6	473 432 457
23-2	11.0 8.1 7.5	135.1 133.7 137.1	26.0 26.0 25.0	74.6 72.6 80.0	695 587 509	26-1	9.3 9.2 9.1	112.2 108.9 127.1	14.3 14.2 14.1	40.4 38.2 45.6	473 432 457
13-4	13.1 13.3 13.1	124.1 124.6 139.6	20.0 19.5 19.0	80.6 88.2 95.2	456 471 452	26-1	9.3 9.2 9.1	112.2 108.9 127.1	14.3 14.2 14.1	40.4 38.2 45.6	473 432 457
Av.: 130.1						Av.: 121.5					
25.6						75.6					
625.9						625.9					
Omitted in Statistical Treatment of Material.											

Submitted in Statistical Treatment of Material.

RENAL FUNCTION.

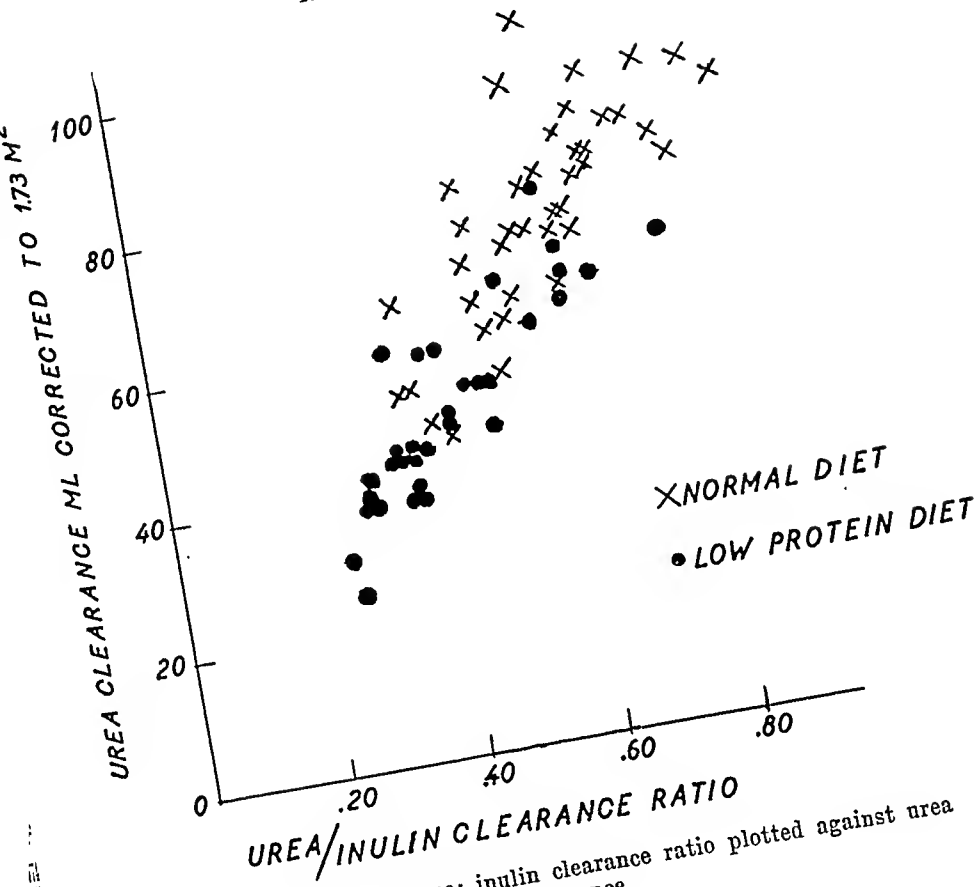


Fig. 1. Urea clearance: inulin clearance ratio plotted against urea clearance.

between the inulin clearance and the diodrast clearance on the two forms of diet is small. In the statistical treatment of the material we have employed only the figures from the final pre-period before the low protein diet, and one extreme value in each of the two groups has been dropped. The probability of a difference in the urea clearance on the two forms of diet lies between 91 and 92 %, whereas conversely, the probability of there being no difference in the inulin clearance is 97 %, and still higher for the diodrast clearance.

These data, and especially the absence of a fall in the inulin clearance and diodrast clearance, very decisively separate the reaction of the human kidney on a low protein diet from that of the dog kidney. Whereas in the dog the ultrafiltration and blood flow vary more or less parallel with the urea clearance, so that the urea clearance: ultrafiltration ratio is almost constant, the fall in the urea clearance in man is registered almost exclusively

by a diminution of the fraction $\frac{\text{u. cl.}}{\text{in. cl.}}$. This becomes particularly clear in fig. 1, where the urea clearance: inulin clearance ratio is plotted as the abscissa, while the corresponding values of the urea clearance are plotted as the ordinate (the values corrected to a surface area of 1.73 sq.m.).

In addition, the tests throw new light upon the effects of diet on nephritis, for there is reason for assuming that the morbid kidney reacts like the healthy one (Cope, Bang (not complete)). Thus we obtain no effect with a low protein diet on the blood flow measured by the diodrast clearance, or on the ultrafiltration, measured by the inulin clearance. For the present we do not know the mechanism which governs the ability of the human kidney to reduce the urea clearance on a low protein diet, whereby the fall of the blood urea is checked.

Summary.

By tests on eight women with healthy kidneys on a normal diet and on a diet poor in protein (nephritis diet) the authors found a drop of 33 % in the urea clearance on the low protein diet, but a simultaneous fall of only 7 % in the inulin clearance and 2 % in the diodrast clearance. Therefore the fall in the urea clearance is conditioned almost exclusively by the reduction of the ratio urea clearance: inulin clearance.

Theorie und Klinik der Nierentätigkeit.

Von

Emerit. Prof. Dr. K. v. BUJNIEWICZ.¹

(Bei der Redaktion am 27. August 1947 eingegangen.)

Im Jahre 1928 habe ich eine eigene Theorie der Harnbildung (und im Jahre 1937 eine eigene Klassifikation der Nephritiden) vorgeschlagen, durch die viele klinische Erscheinungen vielleicht etwas leichter verständlich werden. Diese Theorie zieht die neuen Tatsachen über die partialen Funktionen der Nieren in Betracht und betont die Wichtigkeit der lokalen Diagnostik der partiellen Veränderungen, was meiner Ansicht nach an erste Stelle gestellt werden muss.

Ungeachtet der Meinung Volhards, dass es müssig wäre, sich über den Ort einer Funktionsstörung in den kranken Nieren den Kopf zu zerbrechen, solange man über die örtliche Verteilung der Partialfunktionen in der gesunden Niere nicht im Klaren ist, zerbrachen sich die Kliniker immer noch die Köpfe mit der Lösung dieser so äusserst wichtigen Frage, ohne die eine rationelle Diagnostik, Klassifikation und Therapie der Nierenkrankheiten unmöglich ist. Ihre diesbezüglichen Bestrebungen blieben nicht ohne Erfolg, wie auch ihre Arbeiten auf anderen Gebieten zur Klärung der pathologischen und physiologischen Funktionen verschiedener Organe.

Welcher Ansicht die Physiologen über die Nierenfunktion auch sind, bleiben wir Kliniker doch bei den festgestellten klinischen Tatsachen:

1. Die Retention von Wasser und NaCl beobachtet man bei Erkrankung des Kanälchensystems;
2. Die Retention von Stickstoff beobachtet man bei Erkrankungen des glomerulären Apparates.

¹ Erz. Eugenstrasse 17, Innsbruck (Österreich).

Nach Ludwigs Theorie werden alle Harnbestandteile in den Glomeruli ausgeschieden und in den Kanälchen wird der Harn konzentriert. Nach der Theorie Bowmann-Heidenheins werden in den Glomeruli Wasser und Kochsalz ausgeschieden, in den Kanälchen die übrigen Harnbestandteile. Diese Theorien widersprechen ganz und gar den klinischen Tatsachen. Denn, sollten die Glomeruli wirklich Wasser und Kochsalz ausscheiden, so müsste man, wenn sie geschädigt sind, erwarten, dass die Harnmenge und der Kochsalzgehalt darin vermindert sein werden, die Menge des ausgeschiedenen Harnstoffs und der Urate dagegen nicht; ausserdem müsste man auch erwarten, dass es durch die Wasser- und Kochsalzretention im Organismus zu Oedemerseheinungen kommen wird. In Wirklichkeit aber wissen wir, dass bei Veränderung der Glomeruli, wie z. B. bei sklerotischen Prozessen, gerade das Umgekehrte der Fall ist: die Harnmenge ist gross, der Kochsalzgehalt ist auch vermehrt, dagegen wird der Harnstoff zurückgehalten und es entstehen die azotämischen Zustände mit Urämie, aber eben ohne Oedeme. — Andererseits sehen wir bei Schädigung hauptsächlich der Kanälchen, bei den Nephrosen, dass Harnstoff in genügender Menge ausgeschieden wird, obwohl man eine Retention desselben erwarten sollte. Hier werden das Kochsalz und das Wasser zurückgehalten und es entstehen Oedeme. — Bei dem einen, wie bei dem anderen Typus der Kranken sehen wir klinische und anatomische Ergebnisse, die dem ganz entgegen gesetzt sind, was wir der Theorie nach erwartet hätten. — *Dieser Gegensatz zwischen Theorie und Klinik genügt, um die erwähnten Ansichten über die Harnbildung als unrichtig erkennen zu lassen.*

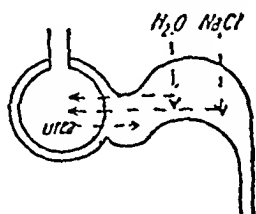
Deshalb möchte ich, mich auf die klinischen Tatsachen beziehend, eine eigene Theorie vorschlagen.

Nach meiner Ansicht wird der Harn in der Weise gebildet, dass in den Kanälchen Wasser und Kochsalz ausgeschieden werden; in den Glomeruli dagegen Harnstoff, Harnsäure u. a. Dabei kommt in den Glomeruli Molekularaustausch zustande: es wird eine äquivalente Menge Kochsalz durch die Glomeruli wiederum aufgenommen, desgleichen auch Wasser resorbiert; so kommt es in den Glomeruli auch zur Konzentrierung des Harns.

Die Rückresorption des in der Kanälchen ausgeschiedenen Kochsalzes durch die Glomeruli und die Abgabe einer äquivalenten Menge verarbeiteter Moleküle hat einen Sinn, sie bedeutet nämlich eine Kräfteersparnis; dem Organismus wird das ihm nötige Kochsalz erhalten und nach den Gesetzen der Diffusion, ohne

unnützen Energieverbrauch, sozusagen gratis, geht die Ausscheidung der verarbeiteten Produkte vor sich. Analog diesem Prozess, der Zirkulation des Kochsalzes in der Niere, verläuft die Zirkulation der Galle im Darmkanal. Denselben Austausch der Moleküle sehen wir zwischen den Blutkörperchen und dem Blutserum, am Peritoneum, an der Darmwand u. s. w.

Harnbildungsschema.



Glomerul., Kanälchen, Henlesche Schleife.

Den Austausch der Moleküle in der Niere kann man sich folgendermassen vorstellen: der Abfluss in der Richtung der Nierenpapillen der durch die Kanälchen ausgeschiedenen Flüssigkeit wird gehemmt durch den Widerstand, den die engen, kapillären Henleschen Schleifen bieten und deshalb geht der Flüssigkeitsstrom auch in der Richtung der Glomeruli, wohin ihn ausserdem die höhere molekulare Konzentration des Glomerulusgebietes anlockt.

Diese meine Theorie ist in vollem Einklang mit den klinischen Tatsachen und macht z. B. folgende Fragen leichter verständlich.

I. Was die *Glomerulonephritiden* betrifft:

Alle Bestrebungen, eine passende Erklärung für die Stickstoff-Retention bei Glomerulonephritiden zu finden, blieben ohne Erfolg. Denn wenn der Stickstoff nach Ansicht der Physiologen durch die Kanälchen ausgeschieden wird, dann müsste, bei Intaktbleiben der Kanälchen bei Glomerulonephritiden keine N-Retention vorhanden sein und anderseits, sollten die Glomeruli Wasser und $NaCl$ ausscheiden, dann müsste infolge Retention von Wasser und $NaCl$ die Harnmenge gering sein. In Wirklichkeit aber beobachtet man bei Glomerulonephritiden gerade das Gegenteil: Stickstoffretention, die Harnmenge dagegen ist nicht nur nicht vermindert, sondern häufig sogar vermehrt.

Eine befriedigende Erklärung, die diese Gegensätze beseitigt, bietet meine Theorie, die 1. Funktion der Kanälchen -- Ausscheidung

von H_2O und $NaCl$, 2. Funktion der Glomeruli — Ausscheidung von Stickstoff und Rückresorption von H_2O und $NaCl$ unterseheidet. Wird nämlich der Stickstoff in den Glomeruli ausgeschieden, so ist es klar, dass bei Herabsetzung oder Ausfall ihrer Funktion eine N-Retention im Organismus zustande kommen muss und als Folge davon eine urämische Intoxikation, Azotämie-Urämie.

Weiters ist es ebenso verständlich, warum die Harnmenge bei Glomerulonephritis oft nicht abnimmt, sondern zunimmt: Die nicht veränderten Kanälchen scheiden das Wasser und $NaCl$ gut aus; wegen der Herabsetzung der zweiten Funktion der Glomeruli dagegen, das heisst wegen der Verminderung der Rückresorption nimmt die Harnmenge zu.

Wenn manchmal bei Glomerulonephritiden Oligurie oder Anurie beobachtet wird, so ist anzunehmen, dass in solchen Fällen das Nierenparenchym stark hyperämisch, geschwollen und komprimiert ist, die Nierenkapsel ad maximum gedehnt und dann jegliche Sekretion der Nieren unmöglich ist; es kann zur völligen Anurie kommen. — In späteren Stadien kann Oligurie dann entstehen, wenn die Nephritis sich ausbreitet, die Kanälchen befällt (Glomerulonephritis cum nephrosi), und ihre Funktion herabsetzt; H_2O und $NaCl$ wird dann in verminderter Menge ausgeschieden, es kann wegen Retention von H_2O und $NaCl$ im Organismus zu starken Oedemen kommen.

II. Was die *Nephrosen* betrifft:

Die tubulären Nephritiden mit Degeneration, hauptsächlich des Epithels der Harnkanälchen, nennt man gewöhnlich Nephrosen, doch wäre es besser, sie in Parallele zur Bezeichnung Glomerulonephritis, Tubulonephritis oder Nephritis tubularis zu nennen; ihre charakteristischen klinischen Symptome sind: Geringe Harnmenge, grosser Eiweissgehalt, viel Nierenepithelien und Zylinder, kein Blut im Harn; Wasser- und Chlorretention im Organismus und starke Oedeme; keine Stickstoffretention und keine urämischen Erscheinungen; keine Blutdruckerhöhung, keine Veränderungen von seiten des Herzens.

Alle diese Krankheitszeichen sind vom Standpunkt meiner Theorie der Harnbildung aus gut zu erklären. Wenn nämlich, wie ich annehme, das Wasser und das $NaCl$ in den Kanälchen und der Harnstoff in den Glomeruli ausgeschieden werden, dann ist verständlich, dass wenn die Kanälchen bei den Nephrosen verändert sind, eine Retention von Wasser und Chlor zustande kom-

men muss, deshalb haben wir wenig Harn und NaCl und wegen ihrer Retention in den Geweben Oedeme. — Der Harnstoff dagegen wird durch die gesunden Glomeruli gut ausgeschieden, es besteht keine Retention von Stickstoff, deshalb auch keine Erscheinungen der Retentionsurämie und oft ein relatives Wohlbefinden des Kranken trotz allgemeiner Anasarca und beinahe Anurie.

Die Oedeme entwickeln sich bei den Nephrosen, glaube ich, deswegen, weil bei den Veränderungen des Blut- und Gewebe-eiweisses unter Einwirkung derselben Schädlichkeit auf das Blut, die gleichzeitig auch eine Nierenerkrankung hervorruft, verlieren die Blutkolloide ihre Eigenschaft, Wasser zu binden; deshalb werden grosse Wassermengen, die vorher in Verbindung mit den Kolloiden waren, frei, können aber durch die erkrankten Nieren nicht entfernt werden, da die Kanälchen, die meiner Ansicht nach Wasser und NaCl auszuschcheiden haben, bei den Nephrosen degeneriert und funktionsunfähig sind. Diese Vorstellung ist, glaube ich, verständlicher als die nichts konkret aussagenden Erklärungen Volhards, wie »eine besondere Bereitschaft zur Wassersucht« oder Transportlipämie.

Auch ist die Lipämie bei den Nephrosen keine Transportlipämie, sie ist eine örtliche Erscheinung, ist Folge der direkten Einwirkung des Virus auf das Blut mit der ausgedehnten Fettdegeneration der Eiweissmoleküle des Blutes und weder Transport noch Import, vielmehr Export erfordert.

III. Das Phänomen *Urina spastica*, die Ausscheidung von Zeit zu Zeit grosser Mengen wässerigen blassen Urins, wird vom Standpunkt meiner Theorie aus folgendermassen verständlich. Wenn, wegen Anregungen usw., es plötzlich zu Spazmen der Glomerulifässe kommt, dann wird die in den Kanälchen ausgeschiedene Flüssigkeit (Wasser + NaCl) von den Glomeruli nicht resorbiert (gleichzeitig der Harnstoff von den Glomeruli nicht ausgeschieden) und diese Flüssigkeit wird fast ganz unverändert und unkonzentriert, in grossen Mengen, als wässriger blasser Harn ausgeschieden, in dem nur Wasser und Kochsalz und fast kein Harnstoff vorhanden ist.

IV. Bei der *Stauungsniere* dagegen wird, je langsamer die Blutzirkulation in der Niere vor sich geht, und je länger der Harn in der Niere verbleibt, um so mehr Wasser und Chlor von den Glo-

meruli aufgenommen und Harnstoff und Urate ausgeschieden; das Ergebnis ist wenig Urin, der reich an Harnstoff und arm an Chlor ist.

Überhaupt stimmt mit dieser Hypothese die bekannte Tatsache überein, dass im Urin zwischen der Urat- und Kochsalzmenge ein Antagonismus besteht. Ist die Uratmenge gross, so ist zu dieser Zeit die Kochsalzmenge gering. Die Hypothese wird ferner durch die Versuche Ludwigs bestätigt, der nach Unterbindung der Ureteren in den Nieren viel Harnstoff, aber fast gar kein Chlor fand.

V. In der letzten Zeit werden immer mehr Fälle der sog. *chloropriven Azotämie* veröffentlicht, bei denen, wegen Chlorverlust im Organismus (Durchfälle, Erbrechen, Ablassen von Ascites u. s. w.) sich urämische Erscheinungen mit hohen Reststickstoffwerten entwickeln. Das Verhältnis zwischen dieser Azotämie und der Hypochlorämie ist ziemlich kompliziert und die Anschauungen darüber sehr verschieden. Ich möchte darauf hinweisen, dass vom Standpunkt meiner Theorie der Harnbildung aus eine Antwort auch auf diese Frage möglich ist.

Die chloroprive Azotämie kann nämlich dadurch erklärt werden, dass für die Ausscheidung des Stickstoffes in den Glomeruli eine genügende Resorption von NaCl nötig ist. Wenn also die Stickstoffausscheidung durch den Molekularaustausch in den Glomeruli bedingt ist, wird die Menge des Stickstoffs im Harn um so geringer sein, je weniger NaCl in der Niere für diesen Austausch vorhanden ist. Bei Kochsalzverlust wird die Menge des NaCl in der Niere (in den Kanälchen) stark herabgesetzt, dementsprechend auch die Stickstoffausscheidung vermindert sein, es kann sich die Azotämie entwickeln.

In solchen Fällen schwindet die Azotämie nach Reehlorierung (z. B. wenn man per os 10 ccm NaCl gibt oder intravenös 20 ccm einer 10—20 % NaCl-Lösung) meiner Meinung nach deshalb, weil die Nieren dann genügend NaCl für die Aufsaugung des Stickstoffs aus den *gesunden* Glomeruli erhalten.

VI. Bei azotämischen, akuten und chronischen Glomerulonephritiden beobachtet man manchmal *Hypochlorämie*, die meiner Ansicht nach dadurch zustande kommt, dass bei der Erkrankung der Glomeruli diese nicht nur keinen Stickstoff ausscheiden, sondern auch NaCl nicht resorbieren; NaCl wird ständig aus dem

Blut durch die unveränderten Kanälchen ausgeschieden aber durch die Glomeruli nicht rückresorbiert; das Blut verliert dadurch reichlich Chlor.

Injektionen von NaCl helfen in diesen Fällen nicht, solange die Glomeruli geschädigt sind, denn der NaCl-Überschuss in den Nieren kann den Stickstoff zur Ausscheidung durch die veränderten Glomeruli nicht zwingen.

VII. Mechanismus der Polyurie bei den Diabetikern und Arteriosklerotikern.

Diabetes insipidus, der als eine endokrine Stoffwechselkrankheit betrachtet wird, und in Beziehung stehen soll mit Erkrankungen des Nervensystems, des Gehirns, der Hypophyse u. a., muss vom Standpunkt meiner Ansicht über die Nierentätigkeit in die funktionellen Nierenerkrankungen als Hypofunktion des glomerulären Apparates eingereiht werden.

Wenn wir annehmen, dass zu der Aufgabe der Glomeruli gehören: 1. Stickstoffausscheidung und 2. Rückresorption der in den Kanälchen ausgeschiedenen Kochsalzlösung, dann ist es verständlich, dass bei Herabsetzung der Funktion der Glomeruli (infolge autoptisch festgestellter fettiger Degeneration des Epithels, oder infolge funktioneller Insuffizienz durch zentralkervöse Störungen, Angiospasmen in den Glomeruli u. a.) die Resorption von Wasser und NaCl und die Ausscheidung von Harnstoff herabgesetzt sein muss, und wie bei *Urina spastica*, wird die in den Kanälchen ausgeschiedene Flüssigkeit (Wasser + NaCl) fast gänzlich unverändert und unkonzentriert in grossen Mengen als blasser, harnstoffarmer Harn ausgeschieden.

Die Erkrankungen des Nervensystems, des Gehirns, der Hypophyse (Gehirnerschütterungen, syphilitische Affektionen, Krebsmetastasen in der Hypophyse, traumatische Neurose u. a.) rufen den *Diabetes insipidus* dadurch hervor, dass sie auf reflektorischem Wege Angiospasmen der Glomeruli auslösen.

Das Opium wirkt dabei günstig als Spasmolyticum, das die Resorptionsfähigkeit der Glomeruli verbessert.

Die von mir bei zufälligen Fiebererkrankungen im Verlaufe des *Diabetes insipidus* beobachteten Besserungen (Abnahme des Durstes im Temperaturanstieg — das Wasser wurde sogar widerwärtig — Sinken der Harnmenge von 8 auf 1,5—2 Liter und Anstieg des spez. Gewichts von 1,001 bis auf 1,010—1,012) kann ich dadurch erklären, dass unter dem Einfluss des Fiebers eine all-

gemeine Erweiterung der peripheren und der Glomeruligefässe eintritt und dabei ihre Resorptionsfähigkeit verbessert.

VIII. Auf etwas andere Weise entsteht m. E. die Polyurie bei *Diabetes mellitus*. Die in den Kanälchen ausgeschiedene Flüssigkeit hat bei Diabetikern infolge der Zuckerausscheidung sicher eine erhöhte molekulare Konzentration. Aus der konzentrierten Lösung vom spez. Gewicht 1,030—1,060 kann das Wasser nicht in das Blut der Glomeruli (Spez. Gewicht des Blutserums 1,010) diffundieren, weil Wasser bei osmotischen Prozessen nach der Stelle der höheren Konzentration zuströmen pflegt. So fällt die Wasserresorption in den Glomeruli bei *Diabetes mellitus* aus und es werden mit dem Zucker die grossen Harnmengen ausgeschieden.

IX. Überhaupt weist eine Polyurie meiner Ansicht nach immer darauf hin, dass die Fähigkeit der Glomeruli, das Wasser zu resorbieren, gestört ist, sei es wegen Spasmen der Glomeruliarteriolen oder wegen organischer Veränderungen der Glomeruli. Das gilt gleicher Weise auch für die akuten Anfälle von *Urina spastica* wie für die *Dauer-Polyurie bei Arteriosklerotikern*.

Auf eine Insuffizienz des linken Herzventrikels antwortet der Organismus bekanntlich mit einer ganzen Reihe von Schutzmassnahmen, um erstens den Blutandrang ins Herz zu vermindern, und zweitens möglichst viel Wasser aus dem Organismus durch die Haut, den Darm und besonders durch die Nieren auszuschcheiden.

Besonders beobachtet man Polyurie bei erschwerter Herztätigkeit bei Arteriosklerotikern und Hypertonikern. Diese Polyurie entsteht meiner Meinung nach so, dass sich am Anfang, im vorsklerotischen Stadium, von Zeit zu Zeit Spasmen der Glomerulikapillaren einstellen; dann kann das in den Kanälchen ausgeschiedene Wasser durch die Glomeruligefässe nicht wieder aufgenommen werden und erscheint in grosser Menge als dünner, wässriger Harn. — Mit der Zeit wird dieser Zustand fixiert, weil sich chronische sklerotische Veränderungen der Glomeruligefässe ausbilden, welche die Resorption von Wasser fast unmöglich machen. Es kommt zur Dauerpolyurie.

Die Veränderung der Blutgefässe der Glomeruli bei Hypertonikern bedeutet eine Ausgleicherseheinung zur Entfernung von möglichst viel Flüssigkeit und dadurch zur Bewahrung des belasteten Herzens vor allzugrossem Blutandrang. Die Sklerose der

Glomeruli ist m. E. also nicht die Ursache der Hypertonie, sondern umgekehrt, sie entwickelt sich als Folge der Hypertonie, als eine Anpassung des Organismus an die erschwerten Kreislaufverhältnisse.

Meine Theorie wurde im Januar 1928 veröffentlicht. Vier Monate später, im April 1928, führte Chevallier, vom Physiologischen Institut von Prof. Roger, in »Paris médical« Nr. 16 eine Reihe von experimentellen Tatsachen an, durch welche bekräftigt wird, dass die Glomeruli Resorptionsorgane sind, woraus er folgenden Schluss zieht: »Die Hypothese von der Rückresorption in den Glomeruli ist sehr wertvoll. Das Experiment zeigt, dass die in den Kanälchen ausgeschiedene Flüssigkeit zu den Glomeruli aufsteigt. Turchini hat das bei Froschlarven wegen der Durchsichtigkeit ihrer Nieren unmittelbar beobachtet. . . Die von Richards und Walker mittels Eisen, chinesischer Tusche und anderen Farbstoffen ausgeführten Experimente lassen keinen Zweifel am Vorhandensein einer solchen Rückresorption. Die Endothelialzellen der Glomeruli nehmen Wasser und verschiedene Stoffe in sich auf, da sie die Fähigkeit der Makrophagen besitzen oder, in moderner Ausdrucksweise, weil sie zum phagocytären oder retikuloendothelialen System gehören.«

Auf solche Weise wurde meine auf klinischer Basis beruhende Idee auch durch das Experiment bestätigt und von den Klinikern ziemlich warm aufgenommen. Sie könnte vielleicht etwas Klarheit in dies sehr verwickelte und unklare Gebiet der inneren Pathologie bringen, da über den Prozess der Harnbildung keine klare Ansicht vorhanden ist. Hier einige Meinungen der Kliniker und Physiologen über meine Theorie: »Erklärt sie doch in ausserordentlich befriedigender Weise das pathologische Geschehen, welches wir am Krankenbett täglich beobachten können« (Kohlschütter, Hamburg); »die sehr viel von den unklaren und verwickelten Vorgängen in der Niere verstehen lehrt« (Neustätter, Berlin); »Jeder, der etwas in der Nierenpathologie versteht, muss zugeben, dass diese Theorie alle klinischen Tatsachen restlos erklärt« (Komarov, Montreal). »Es besteht kein Zweifel, dass Ihre Auffassung nicht nur vom klinischen, sondern auch vom experimentellen Standpunkt sehr gute Unterlagen hat« (Rothlin, Basel). »La théorie que Vous énoncez me paraît des plus séduisantes et conforme aux constatations histo-pathologiques qui mériteraient d'être revues sous ce nouvel angle« (Louis Berger, Quebec). Prof. Stadler nennt sie: »die neuerdings viel Anklang findende Theorie der Harnbildung«. Prof. Assmann (Königsberg) schreibt, dass sie eine weitgehende Anerkennung gefunden hat. In der französischen Fachpresse schrieb man unter anderem: »Si une théorie est vraie, quand elle explique tous les faits observés et n'est en contradiction avec aucun, on peut dire que nous tenons une explication synthétique et vraie de la physiologie rénale« (G. Batier, Strassburg).

Dabei kann ich noch hinzufügen, dass ein so erfahrener Forscher wie A. v. Korányi (Budapest), der früher mit Haidenhain die Wasser- und Kochsalzausscheidung als glomeruläre, die Stickstoffausscheidung

aber als tubuläre Funktion anerkannte, in seinen Vorlesungen, die zwei Jahre nach der Veröffentlichung meiner Theorie erschienen, im Gegensatz zu seiner früheren Meinung über die Harnbildung (siehe Z. f. kl. Med. 1898), jetzt ganz im Sinne meiner Auffassung schreibt: »Heute kann es nicht mehr bezweifelt werden, dass die Insuffizienz der Wasser- und Kochsalsausscheidung tubulär-epitheliale, die Störung der Stickstoffausscheidung glomeruläre Symptome sind. Dadurch aber, dass wir sie lokalisatorisch verwenden können, sind wir um einen gewaltigen Schritt vorwärts gekommen.«

Summary.

In the opinion of the author, water and common salt are secreted in the canaliculi. Among the tasks of the glomeruli are: 1. N secretion and 2. reabsorption of the H_2O and $NaCl$ secreted in the canaliculi, the Henle's loops performing the rôle of a «Stau» apparatus. The theory is in consonance with the actual clinical facts. Thus it is possible to understand: *In the case of glomerulonephritis*: N-retention and uremia due to injury to the glomeruli, without water or chlorine retention, as the canaliculi are intact, and no oedema. — *In the case of nephrosis*: water and chlorine retention, oliguria, oedema, due to injury to the canaliculi, without azotemia-uremia, since the intact glomeruli secrete sufficient nitrogen. — In the case of nephrosis, oedema appears because the blood colloids (when the protein of the blood is destroyed under the influence of the harmful effect on the blood, which at the same time gives rise to an affection of the kidneys) lose their property of binding water, and therefore large quantities of water are freed but cannot be removed, since, when nephritis is present, the canaliculi, which secrete water and $NaCl$, are degenerated and do not function. — The lipemia is not a transport lipemia, as Volhard thinks; it is a result of the extensive fatty degeneration of the protein molecules of the blood and requires no transport, but rather export. — *In the case of stasis kidney* the longer the urine remains in the kidney, the more H_2O and $NaCl$ is taken up by the glomeruli and the more urate is secreted. The result is little urine, which is rich in urate and poor in chlorine. — *Chloroprive azotemia*, which arises owing to loss of chlorine due to diarrhoea, vomiting, resorption of ascites &c., can be explained by the fact that the N-secretion which is conditioned by the molecular exchange in the glomeruli is the more reduced the less $NaCl$ there is in the kidneys for this exchange. As in such cases the amount

of NaCl in the canaliculi is greatly reduced, the N-secretion must also be reduced, and azotemia may develop. — *Polyuria*, in cases of *urina spastica*, *diabetes insipidus*, persistent polyuria of the hypertonics arises thus: owing to the spasm or owing to the organic changes in the glomeruli vessels, the fluid ($H_2O + NaCl$) secreted in the canaliculi cannot return through the glomeruli (at the same time as the urea not secreted by the glomeruli) and appears, although quite unchanged and unconcentrated, in great quantities as thinner, more watery urine, containing water and common salt and hardly any urea. — *In cases of diabetes mellitus* the water resorption in the glomeruli is absent, because in osmotic processes water usually flows towards the place of the higher concentration. The water cannot diffuse from the concentrated sugar solution of sp. gr. 1,030—1,060 into the blood of the glomeruli (sp. gr. + the 1,010 of the blood serum), and the great quantity of water is secreted with the sugar.

Book Reviews.

Recent Advances in Clinical Pathology by various authors. General Editor S. C. Dyke M. D. (Oxon.), F. R. C. P. (Lond.). London 1947. J. & A. Churchill Ltd., 104 Gloucester Place, Portman Square. 468 p. Price: 25 shillings (sterling).

This work is produced under the auspices of the European association of clinical pathologists and its idea took shape at a meeting of this association in Oxford 1944. Many medical men and women from continental Europe, seeking refuge in Great Britain from the nazi and fascist tyrannies, played an active part during the war years in building up the British service in clinical pathology. Some of them have contributed to this volume.

The contents are divided into four sections: bacteriology, biochemistry, hematology with cytology, and histology.

From the many chapters of the bacteriology section, edited by Robert Cruickshank, I mention: Laboratory diagnosis of enteric infections, of sore throat, of primary atypical pneumonia, of pertussis, of Brucella infections, of anaerobic infections, of leptospiral infections, laboratory control of chemotherapy.

The section for biochemistry has as editor E. N. Allot. There are chapters, among others, on liver function tests, on control of the blood chemistry in gastro-intestinal disease, on biochemical aids in the diagnosis of nutritional deficiencies, on photoelectric colorimeters et cetera.

The section of hematology and cytology, under editorship of Della Vida (Rome), deals for example with the hematological nomenclature, the transfusion of blood and blood products and problems in connexion with this. One chapter is dedicated to infectious mononucleosis and the differential Paul-Bunnell test, and another to the analysis of the semen.

From the section for histology, edited by Robbe-Smith, I note chapters on aspiration biopsy in general tumour diagnosis, the lymph node biopsy, the wet film technique in neurosurgery.

This book is needed and fills a gap in the modern clinical literature. It can be recommended to every clinician and practitioner.

I. Holmgren.

P. Press & M. Brunner: Tuberkulose-Probleme im Kanton Zürich. 125 pages. Price: Sw. Fr. 10.80. S. Karger, Basel & New York, 1947.

This work was produced at the request of the *Züricher Kantonale Liga gegen die Tuberkulose* and is intended to form the basis of future measures for combating tuberculosis in the canton. It is divided into two parts. The first is predominately statistical with figures for the tbc. morbidity during the year 1945. The second part is based on the medical results of the investigation. The morbidity is calculated on the number of tuberculosis cases treated at nursing institutions and known to dispensaries, and the number of cases is 6,570 — a figure which does not, however, give an exact expression of the position, as it is not based on radiological mass investigations of the population of the canton. From the material, which is carefully worked up according to sex, age and diagnosis, it appears that the morbidity from pulmonary tbc. is 4.5 % (3168).

From a scrutiny of the development of the disease the author has found, *inter alia*, that subsequent to the primary tbc. infection, tuberculosis with some other localization appeared in 14.5 % of the cases. Further, there is a discussion of the first tbc. manifestation, the connection between the primary infection, pleuritis and pulmonary tbc. diagnosed later, and the importance of the collapse therapy for the course of the disease. The establishment of pneumothorax was the most usual surgical measure. The major pulmonary surgical measures were mainly thoracoplasty. It is worthy of remark that, in spite of its great importance for pneumothorax treatment, Jacobæus's method of cauterization of adhesions has not been employed to any considerable extent.

In the second part an account is given of the League's achievements in tbc. work during the 35 years it has been in existence. The activities which have widened in the course of years, have had the result that the contributions from State funds have necessarily had to be increased. Nationalization has been rejected, however, in the first place on the grounds that apprehensions are felt that it would reduce the interest in the work among large sections of the population, and that political influences might have an unfavourable effect on the activities.

The importance of screening is pointed out, and the necessity of the further development and utilization of this important method of examination is emphasized.

The proposal for the establishment of nursing departments intended exclusively for insane and asocial tbc. patients is of special interest.

Naturally the investigation is chiefly of local interest, but the book is worth reading not only for tbc. doctors but also for everyone who is interested in the intensification and development of tbc. work.

Alf Gullbring.

Luigi Condorelli: Fisiopatologia clinica del mediastino. (Sistemazione su base anatomi-fisiologica delle sindromi mediastiniche sensu strictiori). Editor: Luigi Pozzi. Via Sistina. Rome 1947. 163 pag. 80 fig.

The above work was published as a communication from the 48th Congress in Rome, on 22nd—25th October 1947, of the Italian Society for Internal Medicine. It is in the form of a monograph by the author, Professor Luigi Condorelli of Catania with the collaboration of A. Francaviglia and A. Turchetti. The points of view advanced are supported by clear objective documentation, but none the less the work is characterized by a certain personality, the explanation of which is certainly that to a great extent it is the author's own investigations and observations which form the basis of the work.

The fundamental idea in this publication is the following. The mediastinum has previously been somewhat cavalierly dealt with both from the physiological and from the clinical point of view and has been chiefly looked upon as a neutral zone, which certainly contains a number of particularly important organs, but for the rest is of little interest. Against this the authors point out that the mediastinum must be looked upon as a formation with definite physiological tasks, and therefore it also has an anatomical and physiological structure, which is especially adapted to the functional requirements. They also advance a symptom picture which

can be ascribed to pathological changes in the actual mediastinal tissues, a mediastinal symptom complex *sensu strictiori*, with or without a simultaneous affection of the organs enclosed in the mediastinum.

The main physiological functions of the mediastinum are said to be its capacity to accommodate itself to the changes in shape of the thorax during respiration, its capacity to transmit the static and dynamic pressure conditions in the pleural cavities to the organs in the mediastinum, and finally, its task of ensuring for these organs a function independent and undisturbed by their surroundings. The mediastinal symptom picture described refers to disturbances in one or some of these basic physiological functions.

As regards the anatomy, the extreme looseness of the normal mediastinal connective tissue, which allows substances which are fluid or gaseous rapidly and evenly to distribute themselves over the whole mediastinal space, is pointed out. This looseness of the connective tissue forms the foundation of the artificial pneumomediastinum introduced by Condorelli in 1935, which is a valuable addition to roentgenological diagnostics and is stated to be easy to establish and without injurious secondary effects. Further, attention is drawn to the abundance of a special kind of elastic tissue with a structural orientation which is ideally adapted to the functional demands within the different parts of the mediastinum. Condorelli's discovery of a frontally situated septum, which is attached below to the upper part of the pericardium and above continues into aponeurosis cervicalis media is also of particularly great interest and value. This septum completely divides the mediastinum into an anterior and a posterior part, which is of great significance from the diagnostic and therapeutic points of view.

The pathology of the mediastinum in the limited sense is dominated by more or less extensive changes in the mediastinal connective tissue itself, and the accompanying clinical symptoms appear, as has been said above, when the changes are of such a nature or localization that they affect the physiological functions in one direction or another. The pathological changes in the mediastinal connective tissue are seldom primary but are predominatingly *per continuitatem* transmitted from the organs in the mediastinum. The authors point out that a sharp distinction must be made between diseases of the organs situated in the mediastinum and diseases

in the mediastinum itself. To illustrate this distinction it may be adduced that, *e. g.* in itself a luetic aortitis cannot be considered a mediastinal disease as long as it does not exhibit any typical mediastinal symptoms. If, however, the inflammatory process breaks through to the mediastinal tissue and there gives rise to inflammatory or sclerotic changes, there is a mediastinal affection in the limited sense, and this may exhibit one or several of the typical mediastinal symptoms. It is worthy of remark that even very large tumour formations, such as dermoid cysts, etc. only very rarely evoke mediastinal symptoms as long as they are benignant. This appears to be due to the circumstance that genuine compression symptoms do not make their appearance owing to the great yieldingness of the connective tissue. On the other hand, in malignant cases even small tumours may evoke mediastinal symptoms, owing to early infiltrative invasion of the mediastinal tissue. In the case of expansive processes therefore the majority of the signs which are usually designated compression symptoms, are in reality signs of affection of the mediastinal tissue itself.

On the whole the mediastinal symptoms may be divided into 3 groups, each referring to the basic physiological function which is chiefly disturbed. Thus in the first group may be included signs of restriction in the movements of the thorax during respiration, owing to deficient elasticity in the mediastinal tissue. Such signs appear with special conspicuousness in the case of the sternum and diaphragm. Abnormal respiratory movements of the organs lying in the mediastinum owing to adhesions, etc. also belong to this group. In the study of these disturbances an artificial pneumo-mediastinum is often of great help, and affords valuable information for physical and roentgenological diagnostics, but can also be employed as a more independent examination method of estimating the capacity and pressure conditions of the mediastinal space.

Disturbances in the static and dynamic pressure conditions affect in the first place the large veins, especially vena cava superior. If the normal negative pressure in the mediastinum decreases, it is also weakened the *vis a fronte*, which is of such great importance for the venous flow to the heart. Only in very advanced cases, however, does a pronounced stasis picture with cyanosis, oedema etc. appear owing to disturbances in this mechanism. Considerably more usual, according to the authors, is a condition of hemodynamic compensation, with spasms and increased pres-

sure in the peripheral veins, typical changes in the venous pressure curve and narrow retinal veins. Only the vena jugularis externa is swollen, owing to its poverty of musculature.

Finally, to the third group are referred signs of decompensated venous stasis and arterial stenoses, owing to compression from infiltrating and sclerosing changes in the mediastinal connective tissue. This group also includes stenoses of the air passages with dyspnoea, cough, broneho-spastic crises, etc. Symptoms of irritation and paresis from the nervous system (recurrent paresis, Horner's syndrome, diaphragm paresis, etc.) are also very usual.

Thus this publication presents many interesting and some new points of view in a field which has not previously attracted very great attention, and therefore it constitutes a valuable addition to the literature on this subject. A clear and distinct presentation and a well-balanced arrangement facilitate the reading of this book.

Alvar Gjertz.

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Experiments on Deantigenizing Serum Protein.

By

JENS BING.

(Submitted for publication August 22, 1947.)

Introduction.

Blood transfusion has become so common nowadays that it is difficult to obtain blood in sufficient quantity, and therefore many attempts have been made to produce suitable blood substitutes. Various colloidal solutions have been used for the purpose, the effect of which on being introduced into the blood stream is to increase both the blood volume and the colloid-osmotic pressure. Most of the substances employed are foreign to blood, such as acacia, gelatine, dextran and polyvinylalcohol preparations; but it was also natural to try deantigenized animal serum proteins, which are obtainable in large quantities and which, apart from serving as colloids, may be of value as a source of protein.

The literature contains a number of reports on earlier experimental work on the deantigenizing of serum protein with acids and bases (Wells (16), Ten Broeck (4), Landsteiner & Barron (12), Johnsson & Wormall (11)), and in more recent years it has been taken up by Davis & Eaton (6), Arnow, Kazall & de Falco (1, 9) and Levis (13) who have confirmed the fact that serum protein can be deantigenized by protracted hydrolyzation. It would seem, however, that serum thus treated has not got beyond animal

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experiments to the treatment of patients, no doubt because further tests have shown these preparations either to have preserved their antigenicity or to be toxic. In the course of recent experiments (Bing (2)) it was shown that serum protein can lose its antigenicity on being subjected to lengthy alkaline hydrolysis. At the same time, however, it was also found that the protein changes during the treatment, there being, for instance, the less coagulable protein the longer the alkaline treatment lasted. Moreover, it was shown that the size of the protein molecule had become so small that it was excreted in the urine, so that it is more correct to call such serum proteose than deantigenized protein. That the protein was scarcely broken down farther than to the proteose phase appeared from the fact that it could be salted out with ammonium sulphate and that it was nondialysable through a cellophan membrane. Tests with daily intraperitoneal injections into rats resulted in characteristic changes in the omentum and violent changes in the kidneys, where deposits of proteose were made in the tubules, but the animals tolerated the injections well. But when similar injections were made into rabbits there were several cases of toxic symptoms. It was therefore decided to drop the work on these preparations.

In addition to treating with alkali there have been attempts to deantigenize serum protein by heating after adding formalin (Edwards (7, 8) and Masson (14, 15)). To serum Edwards added 0.20 % by volume of aqueous formaldehyde and then — after shaking the liquid — 0.20 % by volume of 0.88 ammonia, by help of which any excess formaldehyde was converted into hexamine, which is innocuous. The serum was then placed in a waterbath for half an hour, during which the temperature rose to 73° C., whereafter the serum was ready for use. Treated in this manner the serum was found to be deantigenized and atoxic when tested on animals, whereafter it was employed for patients. Edwards states that no injurious by-effects were observed from the intravenous injection of it into 200 patients, and that the preparation was only abandoned because sufficient human serum was available. Physico-chemical analysis showed the preparation to be so altered that all the protein was found to be in the albumin fraction when ultracentrifuged. Its colloid osmotic pressure was somewhat lower than that of human serum.

This method seems to have been employed only by Cordier & Demirleau (5) apart from Edwards. They made no animal tests

but applied the preparation immediately to patients. Of 29 patients given from 400 to 800 cc intravenously, three registered toxic complications — dangerous in one instance — and a fourth patient had oedema and urticaria on the thirteenth day.

Masson (14) employed a method very similar to Edwards'. He added formol until a concentration of 0.36 % was reached, and five minutes later ammonia down to a concentration of 0.01 %. The plasma was then heated over steam, and when it began to boil at 100° C it was left to cool. With this treatment he states that the albumin-globulin ratio is not altered, whereas freezing point and viscosity rise. The colloid osmotic pressure was not measured. Masson states that after heating to 100° C, or better to 110° C, there will be neither precipitinogen nor anaphylaxis-inducing antigen in the serum. Tests were made for these on guinea-pigs, rabbits and dogs. On the other hand there is a possibility of a toxic reaction, which he considers is caused by the formalin. The preparation was employed on more than a thousand patients, some of whom were given repeated injections. In about 3 % there was rigor, but otherwise there were no complications except a transient proteinuria.

Own Investigations.

Technique.

In the present work I have examined the question of whether Edwards' and Masson's experiments on deantigenizing serum protein by heat treatment after adding formalin could be reproduced.

Preparing the serum. Three preparations were made by means of Edwards' technique, which was followed minutely, and five by Masson's, in which I varied the heating temperature and the time, F 4 being heated to 100° C for 10 minutes, F 9 to 100° for 15 minutes, F 12 to 98—100° for 30 minutes, F 15 to 110° C for 5 minutes and F 16 to 110° for 15 minutes. The serum employed came from calves except that for F 9 and F 12, which came from horses.

Method of determining antigenicity. The preparations were tested for precipitinogen and anaphylaxis-inducing antibody contents. The test for precipitinogen was made by sensitizing rabbits first with intravenous and then subcutaneous injection of 5—10 ml of the preparation every fifth day for 22—33 days. The precipitin

Table 1.

Rabbit No.	Sensitizing prepare	Sensitizing time	Serum tested with (and result)		
			Calf serum	Calf serum	F 3 (+ 10-500) F 4 (0)
800 ...	Calf serum	26 days		(+ + + 100), F 2 (+ 500-1000)	
801 ...	"	26 "	"	(+ + + 100), F 2 ((+) 10-1000)	
X ...	"	26 "	"	(+ + 10-500)	
802 ...	Horse serum	26 "	"	(+ +) 10-500)	(+ 100-500)
803 ...	"	26 "	"	(+ + 100-500),	(+ 100-1000)
804 ...	F 1 & F 2	26 "	"	(+ + 500),	(+ 500-1000)
805 ...	"	26 "	"	(+ + 100-500),	(+ 10-1000)
348 ...	"	24 "	"	(+ + 100-500),	(+ 10-100)
365 ...	"	24 "	"	(+ + 100-1000),	(+ 500-1000)
683 ...	"	24 "	"	(+ + 100-500),	(+ 100-500)
686 ...	"	24 "	"	(+ + + 100),	(0)
687 ...	"	24 "	"	(+ + + 100),	(+ 500)
693 ...	"	24 "	"	(+ + 500)	(+) 10-1000)
444 ...	F 4	24 "	"	(+ + 100-500),	(+) 500-5000,
492 ...	"	24 "	"	(+ + 500-1000),	(+ 500-1000)
599 ...	"	24 "	"	(+ 100-1000),	(+ 1000-5000)
601 ...	"	24 "	"	(+ + 500-1000),	(+) 500-5000
854 ...	F 9	33 "	"	(+ + 500),	(+) 500)
855 ...	"	33 "	"	(+ + 100-1000),	(+ 500-1000)
856 ...	"	33 "	"	(+ + 100-1000),	(+ 500-1000)
860 ...	F 12	33 "	"	(+ + 100),	(+ 500-1000)
861 ...	"	33 "	"	(+ + + 100),	(+ 100)
862 ...	"	21 "	"	(+ + + 100),	
859 ...	F 16		"		

The table gives the result of the precipitation tests. The results are given in parenthesis in which the highest degree of precipitation and the antigen dilution or dilutions, at which the maximum values were found, are given.

Table 2.

No.	Weight	Sensitizing Preparate	Sensitizing time	Dosis, preparate and place of injection in shock test	Result
119	430 g	Calf serum	36 days	1.5 ml Calf serum i. v.	Dead after 3 min.
120	700 g	" "	36 "	1.0 " " " i. e.	Weak reaction.
121	427 g	" "	36 "	2.0 " " " i. e.	Dead.
122	350 g	Horse serum	36 "	1.0 " Horse serum i. v.	Dead after 5 min.
123	510 g	" "	36 "	3.5 " " " i. v.	Dead after 4 min.
125	461 g	F 1	34 "	5.0 " F 2 i. v.	Dead after 5 min.
126	610 g	" "	34 "	1.5 " " i. v.	Weak reaction.
725	545 g	Calf serum	28 "	1.0 " Calf serum i. v.	Weak reaction.
726	550 g	" "	28 "	1.5 " " " i. v.	Dead after 5 min.
727	650 g	" "	28 "	2.0 " F 3. i. v.	Weak reaction.
728	580 g	" "	28 "	2.0 " F 3. i. v.	Doubtful reaction
729	510 g	" "	28 "	3.5 " F 4. i. v.	Strong reaction
730	540 g	" "	28 "	1.0 " F 4. i. v.	Strong reaction.
731	484 g	F 3	28 "	2.0 " F 3. i. v.	Dead after 6 min.
732	580 g	" "	28 "	2.0 " F 3. i. v.	Weak reaction.
733	610 g	" "	28 "	1.5 " Calf serum i. v.	Dead after 4 min.
734	555 g	" "	28 "	1.5 " " " i. v.	Dead after 5 min.
735	590 g	F 4	28 "	3.5 " F 4. i. v.	Dead after 4 min.
737	540 g	" "	28 "	3.5 " F 4. i. v.	Dead after 4 min.
738	530 g	" "	28 "	1.5 " Calf serum i. v.	Dead after 5 min.
739	550 g	" "	28 "	1.5 " " " i. v.	Dead after 3 min.
506	430 g	" "	25 "	1.0 " Horse serum i. v.	Dead after 4 min.
507	409 g	" "	25 "	0.5 " F 9 i. v.	Strong reaction.
509	359 g	" "	25 "	0.5 " Horse serum i. v.	Dead after 5 min.
A	310 g	Control		1.0 " " " i. v.	No reaction.
510	332 g	F 9	25 "	1.0 " F 9. i. v.	Dead after 5 min.
511	357 g	" "	25 "	1.0 " F 9. i. v.	Dead after 8 min.
512	358 g	Control		1.0 " F 9. i. v.	Weak reaction.
514	540 g	F 12	36 "	1.5 " F 12. i. v.	Dead after 6 1/2 min.
515	400 g	" "	36 "	1.5 " Horse serum i. v.	Dead after 5 min.
516	500 g	" "	36 "	1.0 " " " i. v.	Dead after 8 min.
518	322 g	" "	36 "	1.0 " F 12. i. v.	Dead after 45 min.
519	510 g	Control		1.5 " F 12. i. v.	Strong reaction, but kept alive.
B					
3	300 g	" "		1.0 " Horse serum i. v.	No reaction.
8	405 g	F 15	23 "	1.0 " F 15. i. v.	Dead after 2 1/2 min.
9	441 g	" "	23 "	1.5 " F 15. i. v.	Dead after 24 hours.
15	459 g	Control		3.0 " F 15. i. v.	No reaction.
16	403 g	F 16	21 "	0.9 " F 16. i. v.	Weak reaction
20	820 g	" "	21 "	2.0 " F 16. i. v.	Weak reaction
C					
10	484 g	Control		4.0 " F 16. i. v.	No reaction
11	302 g	" "		1.5 " F 16. i. v.	No reaction.
13	374 g	F 15	24 "	1.0 " Calf serum i. v.	No reaction.
17	508 g	" "	24 "	1.0 " " " i. v.	Weak reaction.
17	565 g	F 16	24 "	1.5 " " " i. v.	Weak reaction.
18	408 g	" "	24 "	2.0 " " " i. v.	Weak reaction.
				1.0 " Ox serum i. v.	Weak reaction.

The table gives the result of the anaphylaxis tests on guinea pigs after intravenous (i. v.) or intracordial (i. e.) injection on sensitized guinea pigs and control animals.

Table

Preparate	Treatment	Total Protein %	Albumin %	Globulin %
F 1	Edward's method	3.83	0.38	2.45
F 2	—	5.08	0.43	4.65
F 3	—	4.21	0.59	3.63
F 4	Masson's method.	2.45	0.05	2.40
F 9	—	6.77	0.29	6.48
F 12	—	6.60	0.17	6.43
F 15	—	6.22	0.14	6.08
F 16	—	6.07	0.24	5.83

The table gives the result of the different *chemical tests* of the treated

reaction was performed by mixing 0.1 ml rabbit serum with 0.5 ml antigen dilution, shaking, and then leaving for 90 minutes at 37° C, followed by 4° C until the following day. The following antigen dilutions were employed: 1:10, 1:100, 1:500, 1:1000 and 1:5000. In the case of preparations with a lower protein concentration than serum I used correspondingly lower dilutions of the antigen. The resulting precipitate was tentatively divided into four groups: (+), +, ++ and ++++. This division of course is a rough one and encumbered with a fairly big error from one test to another, but within the same test it is quite useful. For reasons of space Table 1 gives only the highest degree of precipitation and the antigen dilution or dilutions at which the maximum values were found. The anaphylaxis tests were made on guinea-pigs, which were injected subcutaneously with 5 ml every five days for 28—36 days, whereafter in a few cases I gave an intracardiac injection of 1—2 ml of the antigen, in all the others the same intravenously. The reaction is described as doubtful in a case where there was no more than a slight smacking, as weak for animals with some itching, smacking, sneezing and perhaps slight dyspnoea, and as strong in all more pronounced cases except the fatal shocks, for which the time between injection and death is indicated.

Method of chemical analysis. The protein determination was made by means of Henriques & Klausen's method (10) with Kjeldahl's method, and fractionating the proteins by semisaturation with ammonium sulphate. In these determinations the proteins were calculated from the nitrogen content in a precipitate with tannic acid. The fact that part of this so-called protein was

3.

Relative Alb. %	Protein N in % of total N	Coagulable protein in % of protein	Undialysable protein in % of protein.
10	93		
9	96		
14	89		
2	97	90	
4	95	94	96
3	95	92	93
2	95	94	
4	96	92	92

preparations.

actually break-down products of protein will appear from the following. Coagulable protein was determined by boiling for five minutes after diluting with physiological saline to about 0.3 % protein and adding $\frac{1}{10}$ th by volume of Sørensen's acetate-acetic acid solution.

Result.

Experiments on deantigenizing with Edwards' method were carried out with three preparations, as already stated, though the first two were employed for sensitizing and testing the same animals. As will be seen from Tables 1 and 2, these preparations proved to be distinctly antigenic in both precipitation and anaphylaxis tests, and they sensitized the animals both to the injected preparation itself and to the untreated serum, though with the latter the precipitation reaction was mostly a little weaker. It will also be seen that serum from rabbits sensitized with the untreated serum gave a precipitation reaction with the treated preparations, and that in one case there was a weak reaction in a guinea-pig which, after sensitization with serum, received an intravenous injection of the treated preparation.

Experiments on deantigenizing with Masson's method, carried out with five different preparations, some of which were treated longer than the time suggested by Masson, also showed that the antigenicity was retained in both precipitation and anaphylaxis tests (Tables 1 and 2). Here again there was reaction both with the treated preparation and — mostly weaker — with serum as the antigen. The preparations that were heated to 110° gave a weaker anaphylactic reaction than those heated only to 100°. But in one

precipitation test with a Masson preparation (F 4) and rabbit serum containing antibody against the untreated serum there was no reaction.

Chemical tests of the treated preparations proved them to be less altered than the deantigenized alkali-hydrolysates previously examined (2), inasmuch as 90—94 % of the protein was coagulable and undialysable and the protein nitrogen amounted to 89—96 % of the total nitrogen (Table 3). In contrast to what was the case with Edwards' and Masson's preparations, the proteins in those prepared here were found to precipitate wholly or almost wholly as globulins when semi-saturated with ammonium sulphate.

After repeated intraperitoneal injections of the preparations into rats there was not the same deposition of proteose in the cortical zone as after the injection of alkali-hydrolysate, but similar though slighter changes in more distal parts of the nephrons. A fuller account of these changes and of simultaneous changes in the omentum of the animals, will be given elsewhere (Bing & Teilum (3)).

Summary.

Experiments designed to deantigenize calf and horse serum by adding formalin and heating according to the methods of Edwards and Masson showed that the preparations were still antigenic and thus unsuitable as blood substitutes.

Postscript.

After this MS had gone to press, Melka, Rapant & Zapletal (Lancet 253—382—1947) and Barsoum (Lancet 254—346—1948) reported on investigations which have enabled them to verify Masson's results. In contrast, Boesen, Larsen & Kjerbye Nielsen (Lancet 254—325—1948) report a lowering of the anaphylactogenic effect was obtained only after serum had been treated until the colloid-osmotic pressure was reduced to under 50 %. The difference between the two investigations cannot be due to one group having employed serum and the other plasma, because in tests made since the conclusion of the above I have found that plasma also retains its power of forming precipitin and giving anaphylaxis.

DEANTIGENIZING SERUM PROTEIN.

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From Krohgstøtten Hospital, Oslo. Chief: Einar Blegen, M. D.

A Case of Morgagni-Adams-Stokes Attacks Caused by Transient Recurrent Ventricular Fibrillation Without Apparent Organic Heart Disease.

By

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(Submitted for publication August 28, 1947.)

Ventricular fibrillation (v. fib.) was assumed to be a very probable cause of sudden death in man by MacWilliam (27) as early as in 1889, long before the introduction of the electrocardiograph in clinical practice. He drew this conclusion from experimentally induced v. fib. in animals. Already in 1850 Hoffa & Ludwig (15) had been able to demonstrate how faradisation of the heart in animals led to v. fib. and death. In 1912 Robinson (36) registered electrocardiographically a short period of v. fib. in two patients after clinical death (respectively 4½ min. and 20 min. post mortem) and three years later Halsey (11) reported a longer attack of terminal v. fib. Since then, many cases of terminal v. fib. have been described, in proof of the correctness of MacWilliam's assertion. (13, 18, 28, 48.)

Transient attacks of »well established ventricular fibrillation» were for the first time recorded by Robinson & Bredeck (37) in 1917. The patient had repeated Adams-Stokes attacks, had pronounced cardiac insufficiency and died 30 hours later during a fresh attack. Likewise several cases of transient v. fib. have been reported, especially in recent years. (7, 9, 10, 17, 20, 25, 29, 32, 33, 39, 40, 41, 42, 43, 44, 45, 46, 47, 56, 57.)

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It appears from the reports that the cause both of the terminal and the transient form of ventricular fibrillation is always to be found in an organic disease of the heart, most often coronary sclerosis or thrombosis with infarction. Frequently there is also present heart block in one or other form, and then especially total auriculo-ventricular block. (5, 7, 9, 10, 20, 32, 33, 39, 40, 47, 56.)

It has not been possible to find any electrocardiographically verified case of purely functional transient ventricular fibrillation of somewhat long duration. As early as in 1911 Hoffmann (17) mentions a case of transient v. fib. which was registered at the close of an attack of tachycardia in an apparently healthy young woman. Halsey doubts whether the brief attack of diphasic oscillations (3 seconds) was really a case of v. fib. Rasmussen (34) has in his textbook an electrocardiogram which indistinguishably resembles one of the electrocardiograms (fig. 4) taken from our patient immediately before his attack of v. fib. It presents a succession of ventricular extrasystoles, which is the pathognomonic precursor of v. fib. Rasmussen's patient did not faint during this attack, as it lasted so short a time (about $2\frac{1}{2}$ sec.), but afterwards during his stay in the hospital he had several Adams-Stokes attacks. It is probable that there then existed a well developed v. fib., but the attacks were not registered. As Hoffmann's case, this patient had no organic heart disease. A case described by Bjerlov in 1932 as »A case of ventricular fibrillation recovered», without any Adams-Stokes attack, has later been published by Öhnell (59) as being a Wolff, Parkinson and White syndrome with paroxysmal tachycardia. Between the attacks of tachycardia the electrocardiogram always showed bundle branch block and short P—Q interval. Öhnell has reported a case of W. P. W. syndrome with a similar electrocardiogram (58).

The electrocardiogram here reproduced (fig. 1), which shows a fully developed ventricular fibrillation, may therefore be assumed to portray the only case of purely functional origin that has hitherto been electrocardiographically recorded.

Case Report.

An engineer aged 38 was on $\frac{26}{1}$ 1944 admitted to the Krohgstotten Hospital under the diagnosis: Attacks of syncope. He had previously always been healthy. Had not had rheumatic fever or chorea minor. Had never been short of breath or had swellings in the legs. He had never noticed anything wrong with the heart until in the spring of

1943 he got palpitation, with distinct sensation of throbbing in the stomach, on the neck and in the hands. The palpitation increased after smoking and when he was at rest. After physical exertion he never noticed anything wrong. After he had been troubled with palpitation for a month he consulted a doctor. Nothing pathological was found either on clinical or radiological examination of the heart. Electrocardiograms were not taken. He was all the time at work.

After a transient attack of palpitation in december 1943 the trouble came on again in january 1944 and persisted until his admission to the hospital on 26/1 1944. In the evening of the 24th Jan. he fainted while he was sitting at his writing-table. His wife believed he was unconscious for a couple of minutes. On the evening before admission to the hospital he was on night duty at the Electrical Works and again fainted while sitting at his working-table. Parenthetically, it is to be remarked that he has nothing to do with the high-voltage cables, but has only office work. In the course of the following morning he got four attacks and was then sent to the hospital. On admission he was pale and had cold perspiration. He was looking very bad, but said he felt well both before and after the fainting fits. He fainted 3 or 4 times while he was being examined. Between syncopal seizures, the pulse-rate was about 70 per min., but it rose now and then to 80—90 per min. It was irregular on account of extrasystoles with compensatory pauses, or whole runs of extrasystoles. Just before the attacks the pulse suddenly became impalpable and the respiration ceased. When the pulse had stopped for 8—10 seconds, the patient fainted, without any convulsive movements. Only once were there noticed slight twitchings in the leg muscles immediately after an attack. The pupils were large. No vomiting or passing of bowels or urine. At one time, on listening to the heart while the patient was unconscious, no sounds could be heard, not even auricular sounds although a slow pulsation in a vein on the neck was once observed. An electrocardiogram was taken immediately before, during and after an attack (fig. 1).

This shows first slight sinus arrhythmia with about 70 beats per min. and quite normal appearance. Then come a number of deformed ventricular complexes, starting with an extrasystole. The attack lasts only 2.6 sec. The pulse is impalpable during this time and the patient feels »a little queer», but does not faint. Then we get some extrasystoles again, at first coming separately, then more in succession. Some of the extrasystoles are interpolated. The electrocardiograph is then switched off. Some seconds later the patient again faints and the electrocardiograph is switched on again. The action of the heart is now recorded during a spell of pulselessness, cessation of respiration and loss of consciousness. This part of the electrocardiogram reveals ventricular fibrillation: The ventricular complexes are sometimes fairly regular, but in other parts become more irregular, more flattened and small-waved. P waves cannot be observed.

The recorded attack lasted 17.7 seconds. The cardiac action at the beginning of the attack is 360 and at the end 390 per min.

After the ventricular fibrillation comes a sinusbradycardia (2 re-

volution of the heart) and then possibly auricular fibrillation with total block, or, perhaps more probably, a nodal rhythm with the P waves hidden in the ventricular complexes.

Before we got the film back from the developing room we thought that there probably existed an auriculo-ventricular block, as we had clinically observed the absence of cardiac action and pulse, while we had seen slow venous pulsation on the neck and slow action of the heart after the recorded attack. The patient was therefore given 1 ml. of adrenalin subcutaneously. Fully two hours elapsed before we got the film back. In the meantime the patient had further been given 1 ml. and after half an hour 0.75 ml. of adrenalin subcutaneously, as the attacks continued. We then at last got above-mentioned electrocardiogram and the patient was at once given 0.20 g of quinidine per os. After four hours he had received 0.60 g of quinidine. The syncopes then ceased. He felt only some occasional extrasystolic throbs in the chest during the evening. In the space of 7 hours he had received altogether 1 g of quinidine.

He had in all 10 attacks on the day of admission. The shortest attack lasted 17.7 seconds (the attack recorded on the electrocardiogram), the longest lasted some seconds over $2\frac{1}{2}$ minutes.

The next day he also received 1 g of quinidine per os, but then continued with 0.20 g per day. An electrocardiogram taken that day (fig. 2) shows flattened T waves in the first three leads. Already two days later the electrocardiogram (fig. 3) was quite normal. After a fortnight's stay in the hospital he was discharged in good health on 0.20 g of quinidine three times daily, as he continued to have some extrasystoles.

As regards other examinations made in the hospital it shall be mentioned that the findings over the heart were normal. The blood pressure was 120/80 at several examinations. Radiogram of the heart showed normal conditions. Hemoglobin, red and white blood corpuscles normal. Wassermann reaction negative. Sedimentation rate: 4 mm. Cholesterol in serum: 110 mg per cent. The patient was slightly febrile in the first evening, afterwards afebrile.

After a week he came for control examination. He had been well the whole time, having merely had a few extrasystoles. Incidentally there was recorded a succession of extrasystoles. (Fig. 4.)

At the patient's express wish he was allowed to discontinue taking quinidine. Three months later he was again admitted to the hospital on account of Adams-Stokes attacks. This time none of the attacks were recorded electrocardiographically. The patient was now discharged on 0.10 g of quinidine twice a day, afterwards reduced to 0.10 g daily.

The patient has since come twice for control examination. He is still taking quinidine and is feeling well, has only some extrasystoles now and then. The electrocardiograms are quite normal. The latest was taken on $\frac{5}{1}$ 1947 (fig. 5).

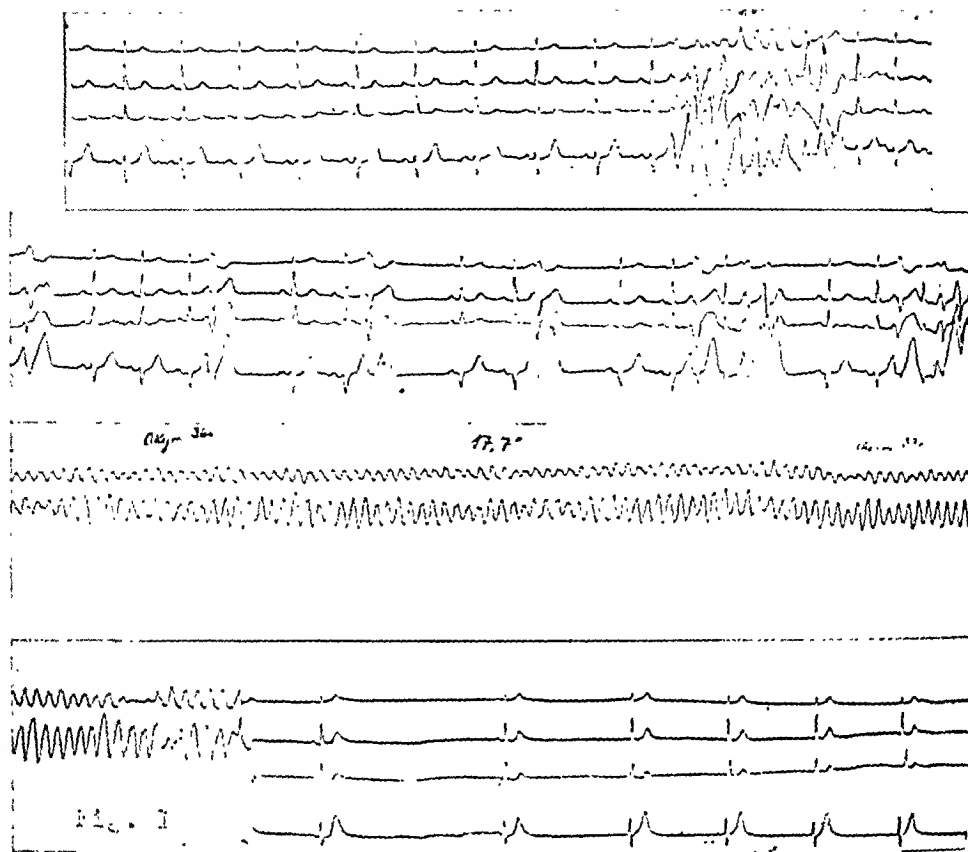


Fig. 1. After a sinus rhythm and a number of deformed ventricular complexes, the electrocardiogram shows ventricular fibrillation and then sinusbradyardia and A—V rhythm. The different parts of the eeg. are following continously except for some seconds just before the patient got the Adams-Stokes attack. When he fainted the electrocardiograph was immediately switched on again.

Discussion.

A good deal of disagreement prevails among the different authors respecting the application of the terms ventricular tachycardia (v. t.) and v. fib. in the electrocardiogram. V. t. may occasionally be seen to pass over to v. fib. and both forms have their pathogenetic foundation in extrasystoles, but there is a distinct difference in the appearance they present in the electrocardiogram. In v. t. the frequency of the pulse may be moderately increased up to about 120, but it may also rise to 300 or more. In v. fib. the frequency may be as low as about 200. Usually it lies between 300 and 600, but it may also be a good

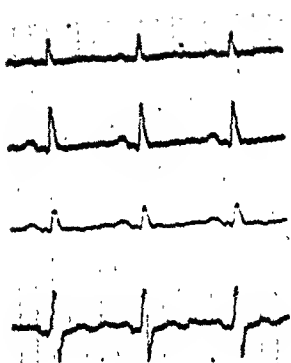


Fig. 2.

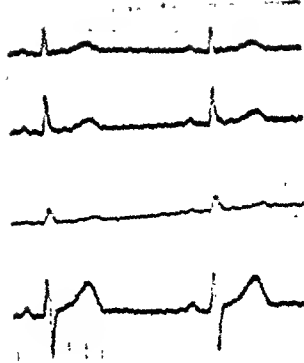


Fig. 3.

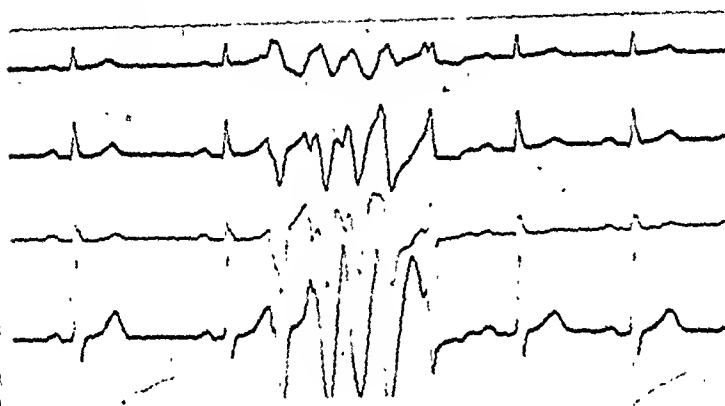


Fig. 4.

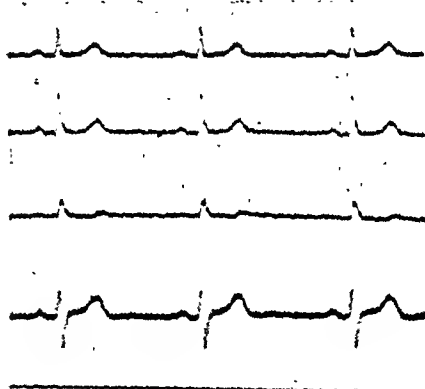


Fig. 5

Fig. 2. The eeg. taken the day after the attack shows flattened T waves in the standard leads.

Fig. 3. Shows a normal eeg. taken 2 days after the attacks.

Fig. 4. At a control examination a week after the attacks the eeg. shows a succession of extrasystoles.

Fig. 5. Eeg. taken 3 years after the attacks is quite normal.

deal higher. It is not so much the height of the frequency as the appearance of the ventricular complexes that decides whether we have to do with v. t. or with v. fib. In v. t. we have the broad ventricular complexes which resemble the ventricular extrasystoles seen in the intervals between the attacks. The action is, practically speaking, regular and, if it varies, it does so in phases of rather long duration. In v. fib. the ventricular complexes are completely deformed and constantly vary in form and size. For the same reason the action also varies in constantly changing phases and may in some periods be impossible to determine, as the complexes then become slurred and cannot be delimited. The picture may be more suggestive of an artefact than of an electrocardiogram.

To designate a transitional form between v. t. and v. fib. several authors (24, 28, 29, 38, 57) employ the term ventricular flutter, in analogy with auricular flutter. Ventricular flutter is said to be characterized by an action of 200 to 300, with quite regular deflections without any isoelectric line between them, being also somewhat higher and more pointed than in v. fib. (resembling the teeth of a saw). But the term ought not to be used to designate an independent form of arrhythmia, as the phenomenon is most often only a phase of v. fib. In the electrocardiogram (fig. 1) we see irregular, rapid oscillations, with partly slurred portions (v. fib.) and more regular deflections (»ventricular flutter«). The latter come especially in the last part of the electrocardiogram. The frequency varies in our case between 360 and 390.

Clinically, v. t. and v. fib. may present the same picture. In v. t. with high frequency or in v. t. with more slow action and with weakened myocardium, we may, as in v. fib., find imperceptible pulse, cessation of breathing, as well as Adams-Stokes attacks, if the seizure lasts long enough. In v. t., even when Adams-Stokes attacks occur, the heart sounds will be heard in the great majority of the cases, whereas in v. fib. they are always absent. In our case the patient fainted during the seizure, respiration ceased, the pulse was imperceptible and no heart sounds could be heard.

In *physiological* respects there is a fundamental difference between the two conditions. In v. t. we still have coördinated cardiac contractions, with little or hardly any peripheral circulation, whereas in v. fib. we find quite incoördinated oscillations without any mechanical effectivity. The transition from v. t. to v. fib.

has been observed on exposed hearts in animals. According to Wenchebach-Winternitz (52) one can note the steady transition from rapid and very weak contractions which pass over to fibrillary twitchings, whereupon the circulation ceases. Afterwards there can be seen a third stage with slow undulatory movements.

Wiggers (54) has given a detailed description of v. fib. in exposed hearts of dogs, illustrated by electrocardiogram and film. He divides the ventricular fibrillation into four stages:

The initial undulatory stage of tachysystole lasts less than one second. Here we still have coördinated contractions. The electrocardiogram shows fairly large deflections in the QRS complex, but they gradually become smaller and the frequency increases to 600—750 per min. The condition then passes over to the second stage, which shows convulsive incoördination and lasts from 15 to 40 seconds. The electrocardiograph shows that the deflections vary greatly in amplitude and duration. The frequency is about 600 per min. In certain sections it may rise to 1,560 per min.

The third stage of tremulous incoördination continues two or three minutes and is of high frequency. On the electrocardiogram it is seen that the QRS complexes increase in frequency up to 1,100—1,700 per min. and decrease in size.

The fourth stage of atonic incoördination is characterized by feeble wavelets of contraction over the whole surface, but by degrees more and more areas become quiescent. The electrocardiogram shows in the beginning large oscillations with a frequency of between 540 and 720. The amplitude gradually decreases and likewise the frequency declines — to 360. Finally, all movement ceases, but small irregular oscillations may still be recorded on the electrocardiogram. Whether these are due to contractions deeper down in the ventricle or to conduction without mechanical effect cannot be decided.

As is seen, the frequency in v. fib. in the dog's heart is very high and is in certain stages much higher than in human beings, in whom however, frequencies of up to 1,000 per min. have been observed.

The *mechanism* of v. t. and v. fib. is no better known than that of auricular flutter and auricular fibrillation. It is supposed that in the ventricle there are one or more over-irritable centres at which there arise extrasystoles or the so-called »circus movement» of the excitation, which again is thought to be evoked by an extrasystole. According to the »circus movement» theory the excitation

wave in ventricular fibrillation would move along a more irregular and smaller pathway than in ventricular tachycardia.

Both in v. t. and in v. fib. the sinus rhythm is usually quite undisturbed. There is total retrograde auricular block, such as we also know from the ventricular extrasystoles in general. In v. fib. we cannot see the P waves in the electrocardiogram, we can at most find a suggestion of their presence. In v. t. the P waves can now and then be seen. On rare occasions in v. t. auricular block may fail to occur, so that there may come an auricular contraction for each ventricular contraction. Or there may be partial block: 2 : 1 or 3 : 1. The auricular rhythm can be observed in exposed animal hearts. Sometimes auricular fibrillation may be present together with v. t.

On the other hand, the supraventricular tachycardias may be difficult to distinguish from the ventricular forms. In both cases the P waves may be hidden in the ventricular complexes and in supraventricular as in ventricular tachycardia we may find broad ventricular complexes, owing to the presence of functional bundle-branch block. Jervell (19) describes a case of infarction in which a functional bundle-branch block occurred during an attack of paroxysmal auricular tachycardia. The case seemed entirely to resemble a paroxysmal v. t., but P waves could just barely be glimpsed before each ventricular complex. Ventricular extrasystole before and after the attack are convincing proofs of the presence of v. t. or v. fib. Likewise a slow venous pulsation on the neck will show that we have here a ventricular and not a supraventricular tachycardia.

What is the reason that v. t. and v. fib. are not recorded more often than is the case, seeing that the foundation thereof lies, as stated above, in the ventricular extrasystoles? Next to sinus arrhythmia these are, as we know the most frequently occurring forms of arrhythmia. That this has not been done is due to several reasons.

In the first place, there is a fundamental difference between the individual ventricular extrasystoles or short paroxysms of such extrasystoles on the one hand and veritable v. t. and v. fib. on the other hand. The firstmentioned conditions are usually of functional origin and are benign, in contrast to the last-named, which are often due to a serious organic disease of the heart. For the same reason we therefore find that v. t. and especially v. fib. is usually an agonal symptom.

On the other hand, ventricular fibrillation, whether of organic or functional cause, is in itself a condition that cannot last for more than some few minutes on account of cerebral anemia. Either death ensues, or else in some rare cases the patient recovers within the time mentioned. We therefore seldom have time to take an electrocardiographic record of v. fib. V. t. is a somewhat more lasting condition — up to 32 days have been noted (6) — and is therefore more often electrocardiographically recorded.

Thirdly, it seems that there must almost always be present one or other form of heart block, and then especially auriculoventricular block, in order that v. fib. may arise. This has been particularly emphasized by American authors (7, 9, 10, 20, 32, 33, 39, 40, 47, 56). Davis and Sprague (5) hold that the auriculoventricular block is the pathogenetic basis for v. fib. and that it is the improvement in the conduction power that brings the fibrillation to an end. Theoretically, say the same authors, one might expect that an eventual «circuit movement» in the ventricle would be interrupted by the excitation wave from the auriculoventricular node. Ventricular fibrillation should thus be due not only to impulses of high frequency in one or more centres, but also to disturbances of conduction. Schwartz (39) states that, if in a patient with total auriculoventricular block there comes a distinct increase of the basal rhythm (for example, from 38 to 65) owing to ventricular extrasystoles, a subsequent syncope will be due to the occurrence of ventricular fibrillation. Rasmussen (35) has produced v. fib. experimentally in exposed hearts of dogs by clamping the pulmonary artery and the aorta. The longer the clamping lasted, the greater became the P—Q interval and finally there came a total block and afterwards v. fib. or ventricular stillstand.

In brief: several factors are required to bring about a v. fib. First of all, there usually exists a serious organic disease of the heart: coronary sclerosis or coronary thrombosis with infarction. The anoxia that ensues leads to greatly increased irritability in the ventricles, and if then for the same reason conductional disturbances arise, and especially total auriculoventricular block, ventricular fibrillation may easily be evoked, owing to the absence of the normal excitation wave that would have rendered the ventricles refractory.

In an organically sound heart with no disturbance in the conducting system it seems to be very difficult for v. fib. to develop.

On the other hand Wiggers believe (54, pag. 537) when it does arise, that recovery is certainly rare in man, as in dogs and other larger animals, when the ventricles are entirely normal. The heart of smaller animals (rat, cat) is more likely to recover spontaneously. V. t. of functional origin has been recorded by several investigators (6, 8, 21) but well established functional v. fib. is not seen to be registered in man. In our case no organic heart disease existed not any form of heart block. A retrograde functional block of course exists during the v. fib. but between the attacks the conducting system is in order. Thus it seems as if the impulses with high frequency are alone sufficient to evoke v. fib. The provocative cause of these functionally conditioned impulses is similar to those which give rise to the ventricular extrasystoles: adrenergic substances, coffee, nicotine (smoking), physical exertions and digitalis.

In this connection it may be mentioned that the case is of particular interest from the fact that it shows how the attacks continue during the administration of adrenalin. It is likewise remarkable that the patient survived so many seizures (16 in all). This again shows that an organically sound heart can withstand even numerous attacks of v. fib.

Of interest is furthermore that several authors (7, 8, 51) mention the negative T waves seen after paroxysmal v. t. and v. fib. They may completely resemble the «coronary» T waves seen after infarction. It is believed that they are due to ischemia of the myocardium owing to the paroxysmal attack. In our case, strange to say, there was no change in the T waves just after the seizure (Fig. 1). When the electrocardiogram was taken several Adams-Stokes attacks had passed on and the electrocardiogram is in its first part completely normal. Not until the next day (Fig. 2) did there come a total flattening of the T waves in all three standard leads and diphaseic T in the 4th lead. Two days later the electrocardiogram (Fig. 3) was completely normal.

We can distinguish two main forms of disturbances in the cardiac rhythm which lead to Adams-Stokes attacks:

1. Disturbances in the conduction of impulses. This will in practice mean ventricular standstill due to auriculoventricular block.

2. Disturbances in the production of impulses. Tachycardia, and then especially ventricular tachycardia or ventricular fibrillation.

In some very rare cases both conditions may arise, namely: either first ventricular standstill and then v. fib., or vice versa.

A very seldom occurring cause (coming under Point 2) of Adams-Stokes attacks S. de Boer (3) mentions suddenly arising ventricular bigeminies, where the pulse rate is reduced to the half and where the frustraneous extrasystoles send too little blood to the brain.

The classical form of Adams-Stokes disease is the auriculoventricular block. The seizure comes, as is known, at the moment of transition from partial to total block in the pre-automatic pause when the ventricle stands still. Very rarely the attack comes on in the established ventricular automatism. Sinusblock and sinoauricular block seldom lead to a Adams-Stokes attack.

When we meet with a case of Adams-Stokes disease we will always be inclined to think first of total auriculoventricular block with ventricular standstill as being the cause thereof, since it is this disturbance of rhythm that is most often recorded in such attacks of syncope. It is now held by several authors (16, 32, 33, 38, 57) that *Adams-Stokes attacks are equally often or even oftener evoked by v. t. or by v. fib.* The reason why this fact is not so often noted presumably is that owing to their transiency the attacks are not electrocardiographically recorded.

Clinically to distinguish ventricular standstill from v. fib. *during the actual attack* is quite impossible, since in both conditions we have pulselessness and absence of heart sounds. In both conditions we may occasionally hear the auricular contraction on slow sinus rhythm, while a slow venous pulse on the neck may also be observed. Thus it is only the electrocardiogram that can tell us what is taking place during the attack. The differential diagnosis is extremely important, since we have here two fundamentally different conditions and therefore two entirely different modes of treatment are demanded. In case of ventricular standstill we must employ stimulances: thumps in the region of the heart, coffeine, adrenalin etc., and for v. fib. quinidine. Pressure on the sinus carotieus is ineffective in case of v. t. and v. fib., as the vagus exerts no influence on the ventricles.

In the time between the attacks we have differential-diagnostic indications in case of ventricular standstill and v. fib. In the latter disease we always have ventricular extrasystoles prior to or after the seizure, either separate or multiple. In ventricular standstill we should have had regular cardiac action of about 30—40 be-

tween the attacks that is to say, when the automatism is established. That this cannot be said with certainty without taking an electrocardiogram is shown by our case. Clinically, we observed, it is true, typical ventricular extrasystoles before the attack, but we also noted slow action of the heart after a seizure (the one which was recorded electrocardiographically). Here the slow pulse rate was found as we have said, to be due to a sinus bradycardia and a subsequent nodal rhythm and not to an idioventricular rhythm as we thought at first.

It is obvious from what has been said above that in the mixed forms: first v. fib. and then ventricular standstill, or vice versa, only the electrocardiogram can decide the matter.

There is some uncertainty as to how long the stoppage of circulation must last before unconsciousness ensues. It depends on several factors: the state of the cerebral arteries, the blood pressure etc. In paroxysmal v. fib. the pulse immediately becomes imperceptible and the patient is as a rule unconscious after 8 or 10 seconds, although according to Schwartz up to 20 seconds may elapse before loss of consciousness takes place in v. fib. In paroxysmal v. t. there is great variation as regards the rapidity with which pulselessness and unconsciousness set in. It depends entirely on whether we have to do with a sound or a diseased heart. Healthy young persons can endure a tachycardia of 300 without losing consciousness (for example in a case of auricular flutter where all auricular contractions are transmitted). Wenchebach-Winterberg (52) has seen a patient who had up to 326 beats per minute without fainting. On the other hand, patients with valvular disease of the heart or serious affections of the cardiac muscle (infarction) may faint when the pulse rate is no higher than 170 (16). Scherf (38) likewise states that unconsciousness may occur at a pulse rate of 180 in case of coronary thrombosis and greatly damaged cardiac muscle. The reason is, of course, that the stroke volume in these cases has beforehand been greatly reduced.

We find reports in the literature of unconsciousness having lasted for from 2 up to 6 minutes without fatal result. Wenchebach-Winternitz (52) report 2 minutes in case of ventricular standstill. They mention, however, a case observed by Bachmann, where the duration was 4 min. The patient was given artificial respiration. Scherf (38) reports 3—4 min., Holzer-Polzer (16) mentions 5 min., while Schwartz and Jezer (40) speaks of a case of v. fib. which lasted no less than 6 minutes. This is the longest

time that has ever been recorded. Wenchebach-Winternitz assume that the reason why the patient does not die in these cases of protracted v. fib. is that there is still maintained a minimal circulation. Levine and Matton (25) report a case of nearly 5 minutes' duration, first v. fib. for $3\frac{1}{2}$ min. and then ventricular standstill for 79 seconds. The longest attack in our case lasted some seconds over $2\frac{1}{2}$ min. before the patient recovered.

While it is certain that v. fib. may be the cause of sudden death, it is no less certain that it may also be a secondary phenomenon before or after clinical death in slowly dying patients and have nothing whatever to do with the cause of death.

In general v. fib. presents a very bad prognosis, as a terminal symptom in many dying patients with infarction. In our case there was found no disease of the heart, either on clinical or radiographic examination and the electrocardiograms taken before or after the attack were normal. The functional character of the disease renders the prognosis more favourable and likewise the fact that he is now living in excellent health 3 years after the attack. One must, however, be somewhat cautious as regards the prognosis, as there is some possibility of a recurrence, since he still has premature ventricular beats which for him mean a danger of v. fib. which is always very serious, regardless of the etiology.

In this connection it is hardly necessary to point out, as has also been done by Wiggers (54), that v. fib. is in itself a functional disorder. All attempts to establish a connection with pathological lesions have been fruitless. When in this article we speak of functionally determined v. fib. or v. fl. of functional origin, it is meant thereby that no symptoms of organic disease of the cardiac muscle as cause of the v. fib. have been found.

Treatment. Quinidine sulphate per os is generally recognized to be an effective remedy in treatment of paroxysmal v. t. and paroxysmal v. fib. Meanwhile, cases have been reported in which v. fib. has been evoked by use of quinidine. This has occurred especially where there has existed a serious myocardiac lesion through coronary thrombosis and where the conduction system was damaged (total auriculoventricular block). Quinidine, as we know, reduces all the functions of the cardiac muscle. If the quinidine has a greater effect in prolonging the conduction time than in prolonging the refractory period, it will be more likely to evoke rather than to prevent or put an end to ventricular fibrillation.

Kerr & Bender (20) believed that quinidine sulphate was the cause of v. fib. in their case, where auricular fibrillation and total auriculoventricular block existed beforehand and where the conducting power presumably became still further impaired. Davis & Sprague (5) mention a similar case, where however, the patient had also been given digitalis, which may have been a contributory factor. Schwartz & Jezer (45) gave small doses of quinidine sulphate intravenously to two patients with auriculoventricular block, who then got transient attacks of v. fib. If ventricular extrasystoles had existed beforehand, the attacks of v. fib. more readily occurred. They therefore mean that quinidine intravenously is contraindicated for patients with a tendency to v. fib. They also maintain that certainly this is the case too when the drug is given by mouth. Jervell (18) reports two cases of v. t., with cardiac infarction in which quinidine was given intravenously. One of the patients collapsed, but afterwards recovered. The other died immediately after the injection. The electrocardiogram here showed v. fib. Jervell draws herefrom the conclusion that we ought to refrain from intravenous injection of quinidine in cases of v. t. and keep to the large doses per os, which are very effective. On the other hand, cases have been reported which proved to be intractable to quinidine per os, whereas intravenous injection produced an immediate improvement. (30.)

White (53) states that there have sometimes been seen strikingly good effects from intravenous injection of quinidine sulphate, but that it is simpler and probably equally effective to give that drug perorally (0.40 g every second hour) or else quinine hydrochloride subcutaneously (0.50 g every second hour until the paroxysms cease). It is reported by Brinchmann (4) that large doses of quinidine have been given by mouth for several years without injurious effects. In purely exceptional cases quinidine given perorally may induce ventricular fibrillation.

Levine (23) showed in experiments on cats that quinidine prevented the onset of v. fib. by increasing the refractory period. He therefore finds it rational to use quinidine in cases of v. fib. But, as appears from what has been said above, it is not possible to apply to diseased human hearts conclusions drawn from the action of a drug on healthy hearts of the animals. Blumenthal & Oppenheim (2) showed by experiments that quinidine renders the heart refractory towards substances that bring on v. fib. More barium chloride was required in order to produce v. fib. when

quinidine was injected. With use of digitalis less barium chloride was needed to call forth v. fib:

As in animals experiments the good effects of quinidine on patients with v. t. and v. fib. is most probably due to the fact that it usually is the prolongation of the refractory period that is the dominating feature. The so-called «sirens movement» may therefore be interrupted and the v. fib. cease. Even though given in small doses (0.20 g per os 5 times in 7 hours) the quinidine in our case is believed to have probably prevented recurrence of the attacks. The patient had, it is true, spontaneously recovered from each attack before he was given quinidine, but the seizures came on again. When he was given quinidine the attacks definitely ceased at the point of time when we should expect the tablets to show an effect. The patient had no recurrence as long as he used quinidine prophylactically but he again got the Adams-Stokes attacks when he omitted to take the tablets. After the last attack he has daily been taking 0.10 g quinidine sulphate per os and has now had no attack for 3 years.

Summary.

1. There is given a brief survey of the earliest reported cases of ventricular fibrillation.

2. A case of numerous Adams-Stokes attacks in a healthy young man is described. The electrocardiogram shows a typical case of ventricular fibrillation with a duration of 17.7 seconds in one of the seizures. The longest attack lasted some seconds over 2½ minutes. The ventricular fibrillation must have been of purely functional origin.

3. The electrocardiographic and clinical differential diagnosis between ventricular tachycardia and ventricular fibrillation is discussed.

4. Further are discussed the pathogenesis of ventricular fibrillation: the hyperirritability of the ventricles (the ventricular extrasystoles) as well as the significance of heart block (especially of the total auriculo-ventricular block). In almost all cases it seems that *both* of these factors must be present in order that ventricular fibrillation may be evoked. In the authors case no form of heart block occurs. The fact that during the ventricular fibrillation there is a functional block retrograde to the auricles

and likewise from the auricles to the ventricles is another matter. Thus in some instances (in this case an apparently sound heart) the hyperirritability may be sufficient to produce ventricular fibrillation. In an organic sound heart it is evidently difficult for v. fib. to arise, even where ventricular extrasystoles are present. One might expect to see v. fib. more often, since one of the pathogenetic factors, and doubtless the most important, is the frequent occurrence of ventricular extrasystoles. The main reason why this is not the case is that the great majority of patients with ventricular extrasystoles have organically sound hearts and there may well occur a succession of benign extrasystoles but no veritable malignant ventricular tachycardia or ventricular fibrillation, which occur especially when there exists an organic disease of the cardiac muscle, particularly coronary thrombosis with or without auriculo-ventricular block. Ventricular fibrillation is undoubtedly often present without being recorded. This is naturally due to the inconstancy of the condition: the patient either dies at once or else he recovers at latest within 5 or 6 minutes.

5. The patient had had 11 Adams-Stokes seizures before it was given any remedies. The case is of interest on account of the spontaneous cessation of the attacks. Cessation of ventricular fibrillation in man is certainly very rare when the ventricles are quite normal. In case of organic disease of the cardiac muscle the prognosis is, of course, still less favourable. The patient survived altogether 16 veritable seizures, of which 10 occurred in the course of ten hours in the hospital. Before the electrocardiogram was seen it was supposed that the attacks were due to auriculoventricular block. The patient was therefore given three injections of adrenalin, during which treatment the attacks continued to occur. He had, in all, 5 attacks after being given adrenalin, that is to say, the ventricular fibrillation subsided spontaneously five times even while he was under the influence of adrenalin. After the electrocardiogram had revealed ventricular fibrillation, the patient was given quinidine, whereupon the attacks ceased once for all.

6. The author emphasizes the importance of the electrocardiogram when it is to be decided during an Adams-Stokes attack whether there exists ventricular standstill or ventricular fibrillation. These two disturbances of rhythm represent two diametrically opposite conditions, which demand two completely different modes of treatment.

7. The use of quinidine for treatment of ventricular fibrillation is discussed. In the author's case it is probable that quinidine per os prevented recurrence of the attacks.

Summary of case report.

A 38-year-old man who had previously always been well, gets attacks of syncope. During the seizures he turns deadly pale, the respiration ceases and the heart sounds become inaudible. One of these attacks was registered electrocardiographically. While he is unconscious the electrocardiogram shows ventricular fibrillation. No sign of organic heart disease can be found, either on clinical, electrocardiographic or X-ray examination. Between the seizures the patient feels well. He is still in good health 3 years after the attacks. This should therefore be regarded as a case of Morgagni-Adams-Stokes syndrome caused by paroxysmal ventricular fibrillation of purely functional origin, and it is the only »well established» case of this kind that has hitherto been registered.

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Studies on the Relation of Pharmacology and Chemotherapeutic Effect of some Sulfanilamide-Derivatives.

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Introduction.

One of the most important problems in the treatment of bacterial diseases with chemotherapeutics, is to find out which chemical substance is responsible for the effect. Laboratory experiments with the pure substance prove, in the case of sulfanilamide and its derivatives, only the existence of a bacteriostatic effect [Julius (a)]. As a rule the substance gives clinically the same results as in the laboratory. But this needs not to be necessary. Prontosil rubrum, for instance, has in vitro no bacteriostatic effect (Domagk, Colebrook); in the human body it exerts without any doubt a therapeutical influence. With Marfanil it is just the contrary: it has no measurable clinical effect, but is highly bacteriostatic in vitro [Julius (b)]. — In vitro it is possible to work with chemical pure substances; in the human body many sulfanilamide-derivatives are changed in structure or broken down. Many compounds are made ineffective by acetylation [Marshall (b), Klein]; others are decomposed so that in some cases effective substances are liberated from ineffective. Prontosil rubrum is a good example for this last possibility; by decomposition sulfanilamide is liberated and is most probably responsible for the

therapeutic effect (Trefouel, Fuller, Kellner, Sisley). In many cases therefore, after the administration of one sulfanilamide compound, different substances are present in the human body. Often it is not certain which of these is the effective one. The concentrations of these different substances are of high importance for exerting a therapeutic effect.

The chemical problems are also numerous. Besides the qualitative or quantitative estimations of the medicament administered, this must be done also, as far as possible, with the decompositions. It may be necessary to analyse mixtures. Up till now exact data are only available of some of the most important chemotherapeutics as sulfanilamide, sulfapyridine, the diazoles, the pyrimidines. The others are either not, or incompletely, studied. Often no informations are given on the methods used, so that controls are impossible. It is of great importance to give complete quantitative figures, otherwise no definite conclusion can be obtained.

It is also of importance to correlate the pharmacology and the chemotherapeutic effect in every individual case. The concentrations in blood and urines may be individually very different. Only in doing so a positive or negative clinical effect may find its explanation.

Fourneau studied for the first time the relation between chemical structure and bacteriostatic effect. He stated that when an amino-group and a radical are placed on a para-position at the benzene-ring, a bacteriostatic effect is seen (fig. 1).

When the amino-group is on the ortho- or on the metaposition this effect is abolished. Replacement of one or both H-atoms of the amino-group by other radicals also derives the substance of its effect. A good example is the acetylation in the human body.

The bacteriostatic effect is greatly increased by inserting a sulfanilamide-group on the place of the radical (R), in the para-position. The simplest compound is sulfanilamide, already synthesised in 1906 by Gelmo. In more recent times one H-atom of the sulfanilamide-group was replaced by different compounds.

Marshall (a) introduced the diazotation and coupling of sulfanilamide to an azo-compound, as a method for quantitative estimation. The reaction is positive with all compounds possessing

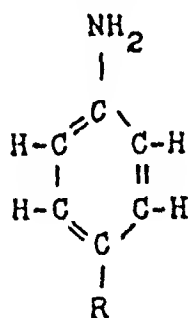


Fig. 1.

a free NH_2 -group attached to the benzene-ring. [Verhagen (b)]. So all sulfanilamide-derivatives, having this chemical structure, can be estimated quantitatively. The reaction is not specific for each of these substances; it indicates only the quantity of a »diazotable substance» present. On the other side is the bacteriostatic effect dependent of the free para-amino-benzene-structure. For this reason the reaction of Marshall and the chemotherapeutic effect often go parallel. As no certainty can be obtained by the reaction of Marshall which substance is present we must assume either the existence of the administered medicament, or speak in general of a diazotable substance. This is exactly the same with the reaction used by Werner. As this reaction was not used by me, further discussion will be omitted.

In spite of Fourné's work, medicaments were introduced not possessing a free amino-group in the para-position. These substances have generally the structures given in fig. 2, 3 and 4.

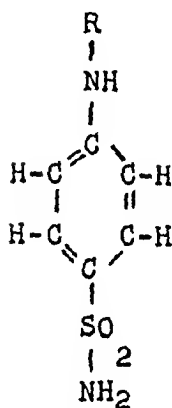


Fig. 2.

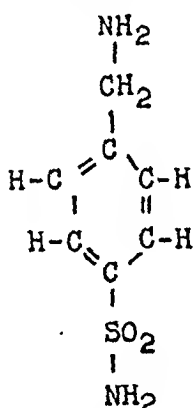


Fig. 3.

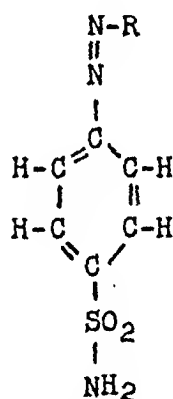


Fig. 4.

They will be the subject of this study.

As the NH_2 -group is either not free, or not attached to the benzene-ring, theoretically no bacteriostatic effect can be expected. A chemotherapeutic effect could be possible when the substance is broken down in the human body to a compound with a free amino-benzene-group. The medicaments of this group give no reaction of Marshall; eventually liberated para-amino-benzene-compounds can be detected and quantitatively estimated by this reaction.

To compare the therapeutic effects, the same disease had to be treated with the different medicaments. The *E. coli*-infection

of the urinary tract seemed to me to be the most appropriate one. The disease is frequently observed, the bacteriologic control of this disease and of the therapeutic effect is easy and reliable; finally is the coli-bacil very sensible to sulfanilamide and some of its derivatives.

Only patients with a chronic, uncomplicated infection of the urinary tract, with a massive bacilluria, were selected. The infection was by the coli-bacil, rarely associated with a second germ. In this case only the effect on the coli-bacil was studied. The patients had a constant bacteriuria, with or without pyuria, during the days or weeks before the treatment; spontaneous recoveries were for this reason unlikely. Almost all the patients were reconvalescent from other diseases, or had diseases not of direct influence on the urinary infection. Nearly all were females, treated in a ward.

Of a fresh specimen of urine (males) or catheter urine (females) was made:

- a native sediment for estimating the number of leucocytes;
- a Gram stained preparation for studying number and type of the microorganisms; only when abundant Gram-negative bacils were present the patient was included;
- a cultural study; with a rare exception Gram-negative bacils were always *E. coli*; later, when war conditions grew difficult, the bacteriologic controls consisted only of the first two mentioned (the cultural work was done by the Rijksinstituut voor de Volksgezondheid).

The patient then received as a rule the medicament in a dosage of three times one gram a day, during three days; when possible a fresh urine-specimen was studied every day; at all events this was done the morning after the last day of treatment. During the whole treatment food and liquids were used freely (Alyea). — Frequent blood-samples were taken; all urines were collected carefully; if possible the concentration of the administered medicament or the products of its metabolism were exactly estimated. The estimations were continued until no further excretion with the urines could be demonstrated. In some cases the patient was treated with different medicaments in succession, including one of the effective ones, to assure the possibility of a bacteriostatic effect.

When not otherwise stated the medicaments were administered

in a dosage of 3×1 gram a day, during 3 days. This was done because of different reasons:

- with the most effective compounds (sulfanilamide, sulfapyridine, sulfathiazol) a positive bacteriostatic effect was always seen; this dosage can be considered sufficiently high. (Alyca.)
- in the medical practice, medicaments of this group are always administered in grams pro die, without taking molecular weights in account;
- when the dosage had been in aequimolecular values, the unfavourable factor of a high molecular weight would not have expressed itself in the clinical results. As will be seen later, some medicaments with a high molecular weight had a dubious bacteriostatic effect: administering aequimolecular quantities would have given a clear positive effect.

In table 1 a summary is given of the different medicaments studied with their molecular weights, the aequimolecular dosage when sulfanilamide is taken as a base for calculation, and the theoretically maximal possible liberation of a diazotable substance.

Table 1.

Medicament	Molecular weight	Aequimolec. dosage with 1 g sulfanilamide	Max. possible liberation of diazot. subst. from 1 gram
Septosil soluble	294	1.71	0.59 (sulfanilamide)
Septazine	262	1.51	0.61 (sulfanilamide)
Soluseptazine	494	2.87	1.00 (soluseptazine)
			0.35 (sulfanilamide)
			depending from accepted struct. formula.
Marfanil	186	1.08	0.00
Acetylsulfamethylpyridine	306	1.72	0.86 (sulfamethyl pyridine)
Prontosil rubrum	291	1.69	0.59 (sulfanilamide)
Prontosil soluble	588	3.42	0.29 (sulfanilamide)
Salazopyrine	398	2.32	0.63 (sulfapyridine)
Pyridacil	249	1.45	0.38 (monoa minobenz)
Neotropine	285	1.65	0.33 (monoa minobenz)

The therapeutic effect was considered positive when during, or immediately after the treatment, no or only a very small number of microorganisms were seen in the gram-preparation; quantitative enumeration of the bacteria was not possible. This does not

mean a complete healing of the infection. Generally the medication must be administered longer than three days to achieve this. Nor was it the aim of these researches; the healing of a urinary infection is a wholly other problem than stating that a sulfanilamide-derivative has a positive or negative chemotherapeutic, c. q. bacteriostatic effect in vivo.

Finally pharmacologic and bacteriologic results will be correlated and a conclusion drawn on the effect, and the substance responsible for this effect. This is not so easy as it seems. We ignore which minimal concentrations are still effective. Rantz, Aleya stated that concentrations of sulfanilamide or sulfapyridine higher than 1.5 mg % in the blood and 25 mg % in the urine gave positive therapeutic effects. For other medicaments no such figures are known. We also ignore if synergisms exist, as Julius (a) demonstrated for sulfanilamide-pyridine. When different substances are present in the human body, this possibility must be beared in mind. Another factor lies in the number of the infecting germs present. In experimental work a bacteriostatic effect is much more pronounced when small numbers of germs are present; a rapid multiplication of the bacteria gives a more pronounced bacteriostatic effect. This factor was never studied in the human being. The constant washing of the breeding place of the germs (bladder, pycnum) gives favourable conditions for rapid multiplication. Probably there are still more factors which have to be taken into account, before a conclusion can be drawn.

This work does not allow a generalisation for other bacterial diseases; they have to be studied individually. The possibility however exists that the conclusions, drawn at the end, are valid for many other infectious diseases treated with sulfanilamides.

Septosil soluble: This medicament is synthesized by Brocades and Stechman (Holland). The structural formula is given in fig. 5.

It is a sodium-succinyl-derivative of sulfanilamide. The substance is a white powder, very soluble in water. Marshall's reaction is negative; after hydrolysing a solution with a strong acid,

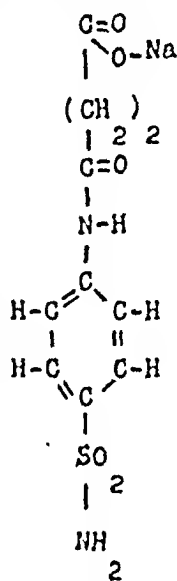


Fig. 5.

it turns to be positive. The hydrolysis induces a detachment of the sodium-succinyl-group from the amino-group, comparable to the liberation of sulfanilamide from mono-acetyl-sulfanilamid (fig. 9). The sulfanilamide liberated gives the reaction of Marshall. Quantitative estimations of septosil-soluble are therefore possible, but only after hydrolysing. — After oral administration, a diazotable substance is present in blood and urines before hydrolysing; so it can not be septosil-soluble. It is therefore very probable that sulfanilamide is liberated in the human body. After hydrolysis the reaction of Marshall increases in concentration; this can either be septosil-soluble or acetyl-sulfanilamide; the last substance being formed out of the liberated sulfanilamide. In the last case we must assume the presence of three substances in blood and urine:

sulfanilamide: estimated before hydrolysis	}	estimated after hydrolysis.
septosil-soluble		
acetyl-sulfanilamide		

A notable difference exists with acetylated sulfanilamides. From these derivatives, also feeble-acid-compounds of the same structure, the human body cannot liberate a free amino-benzene-compound. The reason for this difference is not clear to me.

Two patients with an urinary coli-infection showed no improvement of the bacteriuria during a treatment with 3×1 gram daily. The lack of a therapeutic effect is explained by the very low concentrations of sulfanilamide in the blood; (1.1—1.5 mg %) and urines; (15.3—15.6 mg %) (diazotable products present before hydrolysis).¹

Which part of the increase of the concentrations after hydrolysis (amounting to 108.0—132.5 mg % as septosil-soluble) is given by septosil-soluble, and which part by acetylsulfanilamide, cannot be estimated. The highest possible values for septosil-soluble (as given above when we assume that no acetylsulfanilamide is formed), are also rather low, so that no therapeutic effect can be expected. The total excretion of 85.4—91.2 % (of the administered dose) proves a very good resorption. Still it is an unfavourable medicament; first of all because of its high molecular weight; than because of its breaking down, so that three different substances may be present in the human body: the possible effective

¹ Here and in the future the figures give the highest concentration found during the treatment.

compounds are for this reason present in too low concentrations.

Septazine: Goissedet synthesized this compound in 1936. Specia (Paris) introduced this medicament under this name. The structural formula is given in fig. 6. It is a white powder, very poorly soluble in water (Feinstone).

Suspensions in water of this compound, made from tablets gave a negative reaction of Marshall. No other specific reactions are known to me. It was therefore not possible to estimate septazine quantitatively (Feinstone). As in the preceding investigation, it was of importance to ascertain whether a diazotable product is liberated in the human body and can be the effective agent.

Oral administration of 3 grams daily to two patients, during several days, gave a small concentration and excretion of a diazotable compound, which was partly acetylated again; (in blood: tr.—0.9 mg % free; ± 0.5 mg % acetylated; in urines; 4.1—9.5 mg % free and 5.5—16.3 mg % acetylated; a total excretion of 5.7—10.0 % of the dose in the form of a diazotable substance was observed). In one case a diazotable substance was present in the urines until 7 days after the administration. The patient had no defecation in this time. A very slow resorption is demonstrated by this observation. It seems to me very probable that sulfanilamide is liberated in the human body. First of all because septazine itself gives no reaction of Marshall; secondly because after hydrolysis the reaction increases in intensity, which proves the liberation of a diazotable substance from an acetylated form, which cannot be the case with septazine. Whether septazine exists unchanged in blood and urines, as Long mentioned, could not be decided by me. In this case three substances are present in blood and urines: Septazine; Sulfanilamide; and Acetylsulfanilamide.

The two patients showed no difference in the bacteriuria during the treatment. The extreme low values explain the lack of a therapeutic effect.

In different publications a therapeutic effect with septazine was claimed (Whitbey, Peters). No pharmacologic data are given.

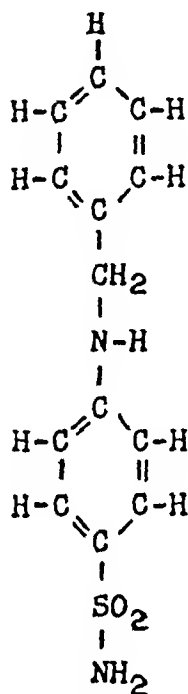


Fig. 6.

My investigations give no explanations for this positive result. Feinstone stated that septazine in mouse-experiments had hardly any therapeutic effect, because of its bad solubility. In a prospectus of Bayer studies of Domagk are quoted in which a therapeutic effect was seen, caused by this medicament, being present in an unchanged form in the human body. The place of the publi-

cation is not mentioned. Britton found no bacteriostatic effect in vitro.

Soluseptazine: This medicament was also synthesized by Goissedet. The firm Specia (Paris), brings the medicament in a commercial form. It is a white powder, very soluble in water. The reaction of the solution is neutral. The structural formula is given in fig. 7 according to the information given by Specia.

According to this structural formula a negative reaction of Marshall is to be expected. In reality it is *positive*. Two explanations are possible; the first supposes that the strong acid, necessary for the diazotation, dissociates the substance in sulfanilamide and a radical. The second assumes that the structural formula is a different one, the radical being attached to the sulfanilamide-group. The last seems to me to be the most probable one. Different arguments stress this view:

a. a radical attached to the free NH_2 -group is not easily liberated by a strong acid; septazine, septosil soluble and acetylsulfanilamide are three examples;

b. a strong acid replaces a radical at the NH_2 -group only when this radical is a feeble acid, and after heating (hydrolysing) as in septosil

soluble or acetylsulfanilamide; the radical in soluseptazine is not a feeble acid, therefore more comparable to septazine, which substance gives a negative reaction of Marshall before and after hydrolysis;

c. after administration of soluseptazine the concentration of a diazotable substance in blood and urines increases after hydrolysis; this means almost certain the liberation of an acetyl-group from the amino-group, which would be impossible if the aminogroup was not free;

d. as will be seen later, a therapeutic effect was observed with this medicament; with a structural formula as given in fig. 7, this effect would be unexplained.

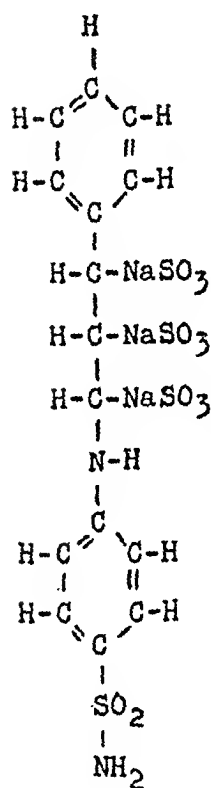


Fig. 7.

As soluseptazine gives a positive reaction of Marshall it is impossible to analyse mixtures with other diazotable substances, e. g. sulfanilamide. Whether sulfanilamide is or is not liberated from this compound, cannot be decided.

Quantitative estimations were performed with Marshall's method, using a 1 mg % standard solution of the pure substance.

After oral administration very small quantities of a diazotable compound were found in the blood and urines. The reason why this so extremely soluble medicament, with neutral reaction of the solution, is so poorly excreted, was not clear to me. Destruction in the human body seems unlikely because of the high concentrations and excretions observed after parenteral administration. After intramuscular administration to one patient, the concentrations in blood and urines were much higher (in blood: 4.5 mg %; in urines: 200.0 mg %), only a small quantity was acetylated (in blood: 0.8 mg %; in urines: 44.0 mg %), which was attributed to the rapid excretion and therefore short time that the medicament circulates in the human body. The total excretion was high; 106.6 % of which 10.2 % in acetylated form.

A clear bacteriostatic effect was seen in the patient.

Marfanil: This medicament was introduced by Bayer. On which theoretical or experimental base it was brought into commerce is not known to me. The structural formula is given in fig. 8. It is a toluol- instead of a benzene-derivative. The substance gives no reaction of Marshall. Other reactions, qualitative or quantitative, are not known to me. On theoretical grounds no liberation of sulfanilamide can be expected.

Two patients treated with Marfanil showed no improvement of the bacteriuria. In none of the blood- or urine-samples a diazotable compound was present. So this therapeutic proved to be without any effect; the possibility of a therapeutic effect by liberating diazotable substances was also absent. Experimental work proved the necessity of a NH_2 -group directly attached to the benzene-ring on a para-position, to have a bacteriostatic effect. Marfanil does not answer to these demands. Curiously enough Julius (b) stated that the substance has in vitro a bacteriostatic effect.

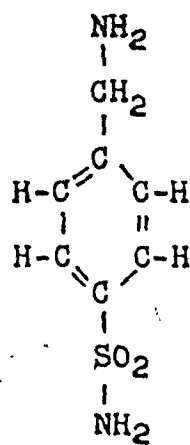


Fig. 8.

Until further studies on this substance prove its value we must

consider the medicament of no clinical importance. The pharmacologic results explain for a part the observed lack of a chemotherapeutic effect.

Acetylsulfamethylpyrimidine: This substance was synthesized on my demand by the Amsterd. Chininefabrick. The structural formula is given in fig. 9. It is a white powder, very poorly soluble in water. The compound has no free NH_2 -group; the reaction of

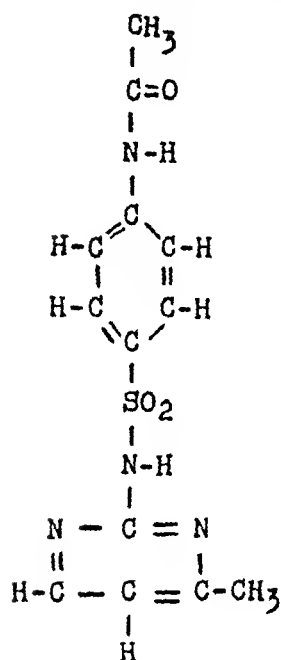


Fig. 9.

Marshall is negative. After hydrolysis with a strong acid the reaction is positive. The intention of this investigation was to ascertain whether the acetylated sulfanilamide-derivatives are de-acetylated in the human body, making the acetylation a reversible process. Klein demonstrated experimentally that the acetylation by liver tissue is not reversible. Shaffer stated that acetylated sulfanilamide-derivatives are de-acetylated in the human body. Sutorius proved a breaking down of acetyl-sulfapyridine in very small quantities to sulfapyridine in one experiment with a patient. My own research concerned two experiments with healthy persons, each receiving 2 grams per os (table 31). Only traces of a free diazotable compound were found, the acetylated product being present in high concentrations (in blood: 2.8—3.5 mg %; in urine: 216.0—380.0 mg %).

The total excretion of 64.7—68.2 % proves a good resorption in the intestines (table 4). From these experiments it may be concluded that the human body liberates sulfanilamides only in a very small degree from their acetates. The chemotherapeutic effect was not studied with this derivative.

The following medicaments are all *Azo-compounds*. They have characteristic colours, which make their recognition easy. Some are indicators which give a valuable control-reaction for their identification. The characteristic colour makes a direct colorimetry possible. With urines this means an easy work; dilution of more than 10 times diminishes the disturbing own colour, even of the most concentrated urines, so far, that it does no more interfere with optic colorimetry. Quantitative estimations in

the blood are much more difficult; the concentrations are low, the own colour and slight haemolysis interfere with the colorimetry; precipitations of the proteins often adsorb the azo-dye and the liberated «diazotable substances». They will be summarized briefly.

Prontosil rubrum: In 1932 this compound was synthesized by Mietsch and Klarer of the I. G. Farbenindustrie, Cologne. Under this name it is brought in a commercial form.

The structural formula is given in fig. 10. It is a red powder, poorly soluble in water; when heated it is a little more soluble. In 96 % alcohol it is fairly well soluble, making standard solutions possible. This solution has an intensive yellow colour, very suitable for optic colorimetry. The reaction of the solution is neutral, the colour is the same in neutral, acid or alkalic milieu. The quantitative estimation of *prontosil rubrum* in urines is done by direct colorimetry. In blood it is done by precipitating the proteins with equal parts of 20 % sulfosalicylic acid; the filtrate contains almost quantitatively *prontosil rubrum*. The diazotable substances are estimated in blood as usually with Marshall's method; the *prontosil rubrum* is present in too low concentrations to disturb. In urines the *prontosil rubrum* is first eliminated by adsorption to leadchloride, which is formed by adding alkalic lead-acetate to the urines. In the almost colourless filtrate, diazotable substances are estimated with Marshall's method.

5 patients were treated; 3 with a positive, 2 with a negative bacteriostatic result. In 4 cases complete figures are available. Table 2 gives the highest observed concentrations in blood and urines of these 4 patients.

In both groups the concentrations of *prontosil rubrum* and sulfanilamide in the blood were exactly the same. In the urines the concentration of free sulfanilamide (diazotable substance) were clearly higher in the cases with a positive bacteriostatic effect; *prontosil rubrum* and the acetylated sulfanilamide showed hardly any difference. These few, but exact observations give strong support to the conception that free sulfanilamide is the effective

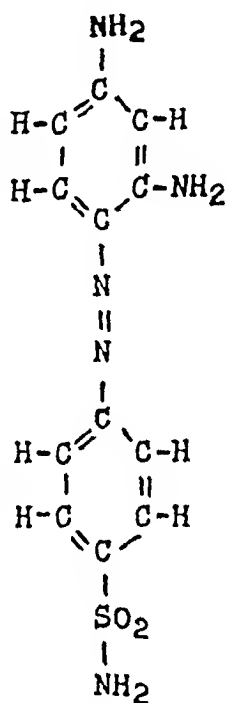


Fig. 10.

agent in prontosil-rubrum-therapy. Interesting is also the statement that not the concentration in the blood but in the urines was decisive for the therapeutic effect.

Table 2.

Case	Concentration in blood in mg %		Concentration in urines in mg %			Bacterio- static effect.
	diazot. subst. free	acetyl.	pront. rubrum	diazot. subst. free	acetyl.	
I ..	1.2	0.3	12.0	39.1	26.5	no effect
II ..	2.2	1.3	36.0	24.4	39.7	no effect
III ..	1.0	0.7	23.2	54.0	11.0	pos. effect
IV ..	2.8	1.9	36.0	68.8	73.7	pos. effect

The favourable and unfavourable results mentioned in the literature (Unshelm, Huber, Borst) find partly an explanation in my observations. In none of the available publications are pharmacological investigations mentioned, partly because Marshall's method was not yet known at that time. It remains therefore uncertain why failures were observed with prontosil rubrum. (Fuller's statement that in infectious diseases prontosil rubrum is decomposed to a higher degree than in normal beings must be considered dubious, because in my, not seriously ill, patients a very variable degree of decomposition of prontosil rubrum was observed.)

My results prove first of all that prontosil rubrum is only present in small quantities; a greater part exists as a diazotable substance (sulfanilamide); this sulfanilamide is partly acetylated. The concentration of prontosil rubrum or sulfanilamide are hardly high enough to produce a bacteriostatic effect. These low concentrations are a result of different unfavourable factors:

- the high molecular weight of prontosil rubrum, which gives lower aequivalents when 3 grams a day are given; (see table 1.)
- the decomposition, so that three different compounds are present; when all prontosil rubrum is decomposed to sulfanilamide, 1.77 grams of sulfanilamide are given pro die; of this dose a smaller or greater part is acetylated; this quantity is the limit of an effective dosage of sulfanilamide.

Prontosil: soluble: This substance was also synthesized by Mietsch and Klarer. Bayer brings the medicament under this

name into commerce. Fig. 11 shows the structural formula. The bright red powder is highly soluble in water.

Prontosil soluble, when injected intramuscularly, was rapidly excreted with the urines, giving high concentrations.

A small concentration and excretion of a diazotable substance was also observed from the beginning. Because of the great molecular weight of prontosil soluble, the small excretion of »sulfanilamide» means still a considerable excretion, when calculated as prontosil soluble. The small concentrations of sulfanil-

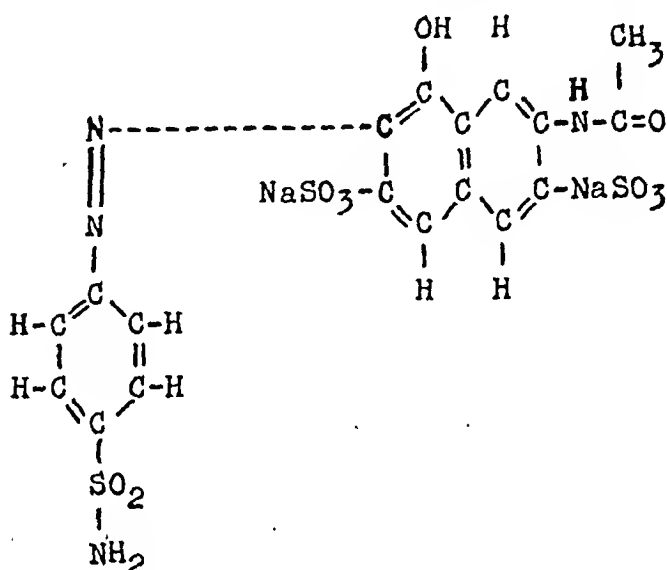


Fig. 11.

amide are well explained by the rapid excretion of prontosil soluble, leaving no time for the human body to decompose it. Fuller and Feinstone stated already that sulfanilamide is liberated from prontosil soluble. Their observations are confirmed by my work. Their quantitative figures however, showing much higher concentrations of sulfanilamide, seem to me not to be accurate. (The chemical methods for quantitative estimations cannot be summarized in short; the author will give detailed informations on demand.)

Two patients with a coli-infection were treated with injections of $2\frac{1}{2}$ gram, divided in 3 parts over the day; they showed no improvement of the bacteriuria. In both cases a high concentration and excretion of prontosil soluble was observed in the urines; (concentration: 68.0—116.0 mg %; excretion: 38.8—77.4 %

as prontosil soluble). The excretion was rapid, for the day after ceasing the medication only a small quantity was excreted. A diazotable substance (assumed to be sulfanilamide), was present in only very small concentrations, of which the total excretion was also very small; (in blood: tr.—0.4 mg %; acetylated: tr.—0.3 mg %; in urines: tr.—4.4 mg %; acetylated: 10.6—15.0 mg %; excretion: 24.9—37.7 % of the medicament as a diazotable substance).

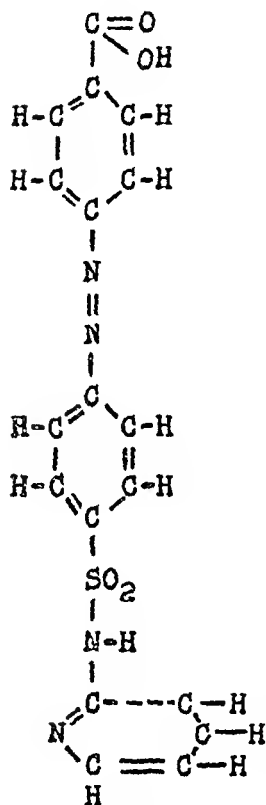


Fig. 12.

Prontosil soluble was present in high enough concentrations to make a therapeutic effect possible. The two observations prove that the compound is ineffective in coli-infections of the urinary tract. The diazotable compound (sulfanilamide) was present in too low concentrations. From the liberation of this compound no results can therefore be expected. These conclusions are the more stressing, because a much higher dosage was given as is recommended by the Firm. The higher molecular weight of this compound is, last of all, also a disadvantage.

Salazopyrine: Askelof and Willstaedt synthesized this compound on the suggestion of Svartz. The N. V. Organon, introduced this medicament in the Netherlands. The structural formula is given in fig. 12. The brown powder is insoluble in water; in diluted sodiumhydroxyde- or

hydrochloric-acid-solutions it solves very well. After neutralisation the substance precipitates again. In alkalic solution it has a bright yellow colour; in acid solution it is colourless (indicator). A standard is prepared by making an alkalic 1 mg % solution.

Quantitative estimations of salazopyrine were done by optic colorimetry in alkalic milieu. In blood this was not possible because of adsorption of the medicament to the protein-precipitate. Quantitative estimations of eventually liberated diazotable substances with Marshall's method were not disturbed by the salazopyrine because it is colourless in acid milieu, in which milieu the reaction of Marshall is performed.

Three patients were treated; in two the bacteriuria disappeared, in one not. The concentrations and excretions of salazopyrine in the urines were very low; (concentration: tr.—9.0 mg %; excretion: tr.—3.6 %). The values for a diazotable substance, assumed to be sulfapyridine, were somewhat higher (in blood: conc. 1.5—2.3 mg % for the free, and 0.8—1.3 mg % for the acetylated form; in urines: conc. free: 12.5—36.0 mg %; acetylated: 30.0—33.3 mg %; excr. 30.6—32.6 % of the administered dose) but still low. It was interesting to state that in the two cases with a positive effect the concentration of free (non-acetylated) sulfapyridine were clearly higher than in the case without a therapeutic effect (resp. 36.0 and 31.5 mg % against 12.5 mg %). The total concentration was in all cases almost equally high; the acetylation was clearly higher in the cases where no therapeutic effect was observed.

These figures allow the conclusion that salazopyrine is badly resorbed and for the most part decomposed in the human body. Because of this last fact a slight effect on the bacteriuria was seen. As 1 gram of salazopyrine can liberate maximally 0.63 gram of sulfapyridine this decreases also the value of this medicament. Svartz and Drukker mention some values in their publications. They also found a diazotable substance in blood and urines. They assumed that it was sulfapyridine. Their pharmacologic observations were incomplete. Urinary infections were not treated.

Pyridium (Pyridacil): This compound was synthesized by Tchitchibabin and introduced by Ostromyslenski as a chemotherapeuticum for urinary infections. The firm Cilag introduced the substance again under the name Pyridacil. The structural formula is given in fig. 13.

It does not contain a sulfanilamide-nucleus. It is a violet-red powder, insoluble in water, very soluble in diluted HCl-solutions. The solution has a bright yellow colour. In acid milieu the colour is stronger than in alkalic. This must be borne in mind when quantitative estimations are performed. Quantitative estimations

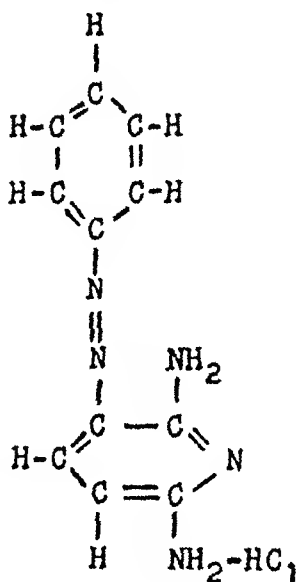


Fig. 13.

of pyridium are performed by colorimetry of the properly diluted urine against a 1 mg % standard of the medicament. In blood it was not possible because of adsorption of the medicament to the protein precipitate.

Three patients were treated with the medicament, 3×1 gram daily. In all cases no effect was observed. Pyridacil was excreted in high concentrations (60.0—110.0 mg %); the total excretion was also high: (56.0—99.0 % of the administered dose). The concentration of 1 mg %, considered high enough to have a bacteriostatic effect (according to the prospectus of the firm), was far exceeded. It seems therefore that the medicament itself has no value. In no instance a diazotable compound was demonstrable in blood and urines. The medicament (according to its chemical structure), cannot liberate sulfanilamide or another diazotable substance; actually it does not liberate these compounds, so no chemotherapeutic effect can be expected from this side.

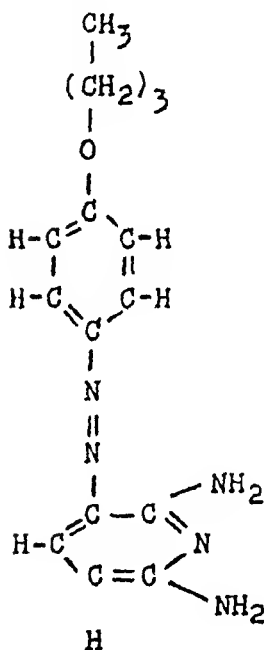


Fig. 14.

Favourable and unfavourable results have been published by Weil, Gillespie, Dimitrief, Walter (summary), Borst (summary). The favourable results have been strongly criticised. The American council on Pharmacy and Chemistry considered the claims for a therapeutic effect not established on positive facts. My experiences afford a further explanation for this missing effect.

Neotropin: This compound is very similar to pyridium. The difference is formed by a butyric-acid-radical attached to the benzene ring (fig. 14). Schering-Kahlbaum introduced this medicament under this name. In water it is insoluble; in diluted hydrochloric acid it solves very well. The pure substance was not available; so a standard solution was prepared from a tablet containing 100 mg.

In acid or alkalic milieu the colour is almost the same. Concerning the quantitative estimations and the qualitative reactions on the presence of diazotable substances, the same can be said as for pyridium and is not repeated.

Two patients were treated with the medicament; 3×1 gram

daily. No effect on the bacteriuria was observed in the treated cases. Neotropin was present in lower concentrations than pyridacil; (18.0—20.0 mg %); the total excretion was also much lower: (25.0—26.1 % of the dose). The administered dose was higher than advocated by the prospectus. So it is dubious whether neotropin has a bacteriostatic effect. None of the urines contained a diazotable product; from this side the medicament proved also to be of no value.

In a discussion on this matter Walter cites german reports on favourable results. The medicament was often used by the same authors working with pyridium, so that exact analysis of the results attributed to the one medicament or the other are not possible. It seems to me that neotropin undergoes the same fate as pyridium.

Summary.

Experimental studies proved that only para-amino-benzene derivatives have a clear bacteriostatic effect. Contrary to these facts a number of sulfanilamide derivatives, which have not a free amino group at the benzene-ring, are still brought into commerce for anti-bacterial treatment. Ten different medicaments are studied in their effect on coli-bacil-infections of the urinary tract of patients. Figures on concentration and excretions of these medicaments, and eventually products of decomposition, were collected from these patients. The author tried by this way to find an explanation for the presence or absence of a bacteriostatic effect.

It was found that no rules can be made. The medicaments were present in very different concentrations in blood, and urines and the total excretion varied also greatly, probably showing a great difference in resorption. Some medicaments were decomposed in the human body, others not. One of the decompositions was in a number of cases a »diazotable substance» (sulfanilamide, sulfapyridine). This substance was partly acetylated again. A bacteriostatic effect was seen only in those cases where a »diazotable» substance, not acetylated, was present in sufficiently high concentrations. The original medicaments exerted almost certainly no anti-bacterial effect.

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This study was finished in the summer 1945: different circumstances postponed the publication.

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The Arteritis Temporalis Syndrome.

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In recent years a new syndrome has appeared to add to the maze of already known diseases of the blood vessels. It has been termed arteritis temporalis. This disease was described for the first time by Horton and Magath (1932) of the Mayo clinic, and since then a number of cases have been reported chiefly in England and America. As there is every reason to believe the disease to be far more common than the published figures show, it might be justifiable to report on the cases hitherto discovered. As we have treated two patients showing a typical clinical picture it might possibly be of interest to follow these cases further.

Case I. A 64 year old woman who had previously been quite well, without significant hereditary history, was taken ill in January 1945. A few days prior to her illness other members of the family had been ill with »flu». The illness began with a rigor in the muscles at the back of her legs, she found it difficult to straighten her legs, particularly on getting up in the morning or after sitting for any length of time. At about the same time she experienced rigors in the neck musculature, especially in the mastoideus sternocleidomastoideus. There was an aching lymphadenitis in the neck and mandibular joints. Some days after being taken ill she felt a shooting pain, of a few moments duration, in the temples and behind her ears. It recurred several times during a period of 24 hours. In March 1945 a tender infiltration, about the size of a sixpenny piece, appeared over the knee joint. It was symmetrical and bilateral. A month later an aching area appeared over each mandibular joint. At about the same time there also appeared swellings, like whip cords, one in each temple, they ached and were tender. Two similar swellings

appeared in the back of the head. All this time she felt more tired than usual and was always cold when resting, but sweated more than before when moving about. The temperature was normal until April, after which time she was subfebril. Sleep was not good. The appetite was poor and the patient lost weight. When she was admitted to hospital on May 3rd 1915 she was in a poor condition, a pale slightly built woman with weak musculature. On examination nothing could be found save a slight tenderness over the mandibular joints and over the superficial temporal arteries of the right side. In the right parietal region some 8 cms above the external auditory canal, there was a very hard and tender infiltration, the size of a pea, and with difficulty moveable over the bone. At the site of the temporal arteries a thin, hard, tender, whip-cord like swelling was palpated. Pulsations were present on both sides. — Laboratory investigations showed a moderate anaemia (Hb 58 %, Sahli), R. B. C:s 3,000,000, W. B. C:s 7,900, differential count normal, B. S. R. 110 m. m. p. h. The skin temperature of the right forearm was lower than that of the left whilst the right leg was somewhat warmer than the left. On June 21st oscillography at rest showed weaker pulsations in the right extremities than in the left. Two weeks later (July 6th) no certain difference in the pulsations in the arms could be found whilst they were a little weaker in the right leg than the left. Oscillography after work gave no indication of organic change in the main arteries of the right leg. Eyeground findings were normal with no vessel changes and no degenerative areas. The clinical findings indicated a case of so called «arteritis temporalis». To confirm the diagnosis a biopsy of the parietal infiltration was made and one month later (June 5th) a further biopsy of the thickened temporal artery was taken. The histological examinations were kindly made by Prof. Hilding Bergstrand and Dr Åke Lindgren. Their report was: «In the excised piece of arteria temporalis, changes characteristic of so called arteritis temporalis, are to be seen. Lumen is almost obliterated by proliferation of the intima in which large endothelial cells rich in protoplasm and fibroblasts are found together with giant cells, akin to foreign body giant cells. A fine collagenous network intersects this new tissue. Elastica and media show isolated defects, filled by proliferation similar to those in the intima and in continuity with these. There are also plasma cells and lymphocytes but no eosinophil cells. There is no fibrinoid necrosis of the wall of the vessel examined, but such necrosis can be seen in the adventitia and surrounding tissue. The changes in both the surrounding tissue and the vessel are typical allergic changes.»

During her stay in hospital (from May to the middle of July 1915) the patient was constantly subfebril and our efforts to combat the persistent infectiouslike condition with the aid of sulphur preparations and penicillin (15,000, later 25,000 O. E. 3 hourly, in all one million O. E.) were unsuccessful. When the patient left the hospital after eleven weeks, she was symptomless but still subfebril and with high a sedimentation rate (E. S. R. 90 mm p. h.). Unfortunately a planned arteriography was for different reasons excluded. One year after being taking ill she reported herself completely free from symptoms.

Case 2. The other case was a spinster of 66; it is known that her mother had asthma and one brother hay fever. The patient herself has had no allergic diseases. On the other hand she has had repeated rheumatic troubles since the age of 25 with periods of pain in the muscles and joints. During 1941—1944 she had pains now and there in the left leg and right foot. These pains had a duration of about 24 hours with a variable free interval. There was no further history of relevant diseases. In December 1946 she became ill and had the symptoms of a cold: coughing and slight headache, but no temperature or pains in the joints. In the middle of January 1947 her condition grew worse and the temperature rose to 39—40 degrees C (102—104 degrees F). Since the beginning of the year she had noticed, that the veins in the temples had swollen, and that the pulse felt hard and throbbing. At about the same time it became difficult for her to open her mouth, but this inconvenience disappeared after some time. Towards the end of January the headache became worse. It was of a boring character but was often interrupted by attacks of shooting or stabbing pains from one temple to the other or upwards towards the vertex or backwards to the back of the neck. The pain was unrelieved by salicylates and was only for a short time eased by morphine derivatives and preparations containing derivatives of barbiturate, salicylate and phenacetin. The temperature was constantly some 38 degrees C (101 degrees F) and the patient appeared quite well during her stay in the hospital. The bruise in the left temple had almost disappeared by the end of February and simultaneously the headache on this side also disappeared. With the exception of the headache the patient had no local symptoms. She was admitted to the medical clinic of Sabbatsberg hospital on March 18th 1947. On examination nothing abnormal was discovered except the local findings. No rheumatic nodules and all joints normal. Blood pressure 115/80. Skin temperature not abnormal. Peripheral vessels: radial artery not rigid. In region of left temple there was a winding, cord like swelling about 3 cm in length, with a somewhat uneven surface, running downwards, and corresponding with the site of the superficial temporal artery; it was very tender. On left side similar changes, although not so marked. No increased heat of the surrounding region and no signs of inflammatory oedema. Pulse palpable on either side. No similar changes in the vessels of other parts of the body, but pulse palpable in the right dorsalis pedis artery.

Laboratory findings: Hb 73 % (Sieca). R. B. C:s 3.7 millions. W. B. C:s 5,800. Differential count: 5 % eosinophil.

Reticuloocytes: 11 per thousand. Serum iron 0.043 mg %. B. S. R. 105 mm p. h. Wassermann, Kahn and Meinicke II negative. Non-protein nitrogen 28 mg %. Antistreptolysin titre: 45 AE/ml. Antistaphylococcal titre: 0.9 units. E. C. G: nothing abnormal discovered but some auricular extrasystoles. Special examinations: normal eye ground findings. Ears, nose and throat normal. All teeth extracted and no roots left. X-ray photo of the neck spine: no spondylitis deformans. X-ray photo of the frontal and maxillary sinuses normal.

After one week (middle of March) the local findings had almost dis-

appeared and to verify the diagnosis a biopsy was taken (one cm long) of the thickened right superficial temporal artery. The specimen was examined by Professor H. Bergstrand (Pathol. Department Sabbatsberg), who stated: »The specimen shows an artery with severe changes in the whole of its length. At each end the destruction is less than in the middle, indicating, that the pathological process is localised in a certain part of the vessels. Within this part the whole circumference of the vessel is affected, contrary to the usual findings in periarteritis nodosa. The pathological process is confined to the intima and media, which are completely destroyed and replaced by granulation tissue, so massive that it fills the lumen of the vessel. There are a great number of giant cells in the granulation tissue with the nuclei in a ring at the periphery. Otherwise the granulation tissue consists of binding tissue and mononuclear cells, but no eosinophil cells or leucocytes. Vessels are present in the granulation tissue, but they are few in number. There are several areas of necrosis in the granulation tissue. Single threads of the binding tissue show fibrinoid degeneration. The elastica interna is totally destroyed, except at each ends, where it still exists. There it is possible to differentiate between intima and media. The media consists of a more »cellrich» granulation tissue and the giant cells are confined to the media, whilst the intima consists of a harder tissue, which is richer on collagen fibres. The picture is in perfect accordance with that described as temporal arteritis.»

The headache was, if possible, still more intense during the few weeks after the resection of the vessels, and on leaving hospital on May 17th 1947 the patient still had moderate and sporadic pains in the left temple region. Otherwise she was completely free from symptoms. A moderate anaemia remained. Hb 66 %. B. S. R. was still very high: 122 mm p. h. As the patient had had pains in her legs an arteriography of right femoral artery had been made. »The femoral artery and the arteries of the leg together with their normal branches are filled. The arteries of the leg are remarkably thin and the contrast passes through them fairly slowly. No further changes are found in the walls.» Angiography of the right internal carotid artery (percutaneous injection): »The internal carotid with its branches within the skull filled. Even the posterior cerebral artery filled with contrast. The vessels rather narrow but no other pathological change to be observed in them. No dislocation of the vessels. No aneurysm.»

When Horton and Magath 1931 published their article »An undescribed form of arteritis of the temporal vessels» they had at the Mayo clinic studied 2 cases of a type of benign sepsis, which could not definitely classified pathologically. When Horton (1937) reported, in all, 7 such cases, it was considered that this was a specific disease, and it was called »arteritis temporalis» due to the local findings always observed in the temporal arteries. Since then other names have been proposed. Oldberg (1941) proposed »arteritis senilis acuta» as the debute of the symptoms

always takes place at an advanced age and arteries other than the temporalis could be affected. The name so far seems fully adequate. The exact frequency of this disease is naturally difficult to ascertain. Most cases have been published in the English speaking countries, partly owing to the fact that the disease was originally described in USA. Some cases in the Scandinavian countries have however been noted. In Sweden one case (Oldberg 1941) and 2 cases with biopsy (Sjövall, Winblad 1944) and in Norway 4 cases (Broeh and Ytrehus 1946) have been reported. The latest publications are to be found in Brit. Med. Journal of August 1946, where the total of known cases is said to be 36. In »Ugeskrift for Læger» Nov. 7th 1946 Torben Andersen gives a detailed survey of the disease and gives a seemingly complete list of the literature. The number of known cases is said to be 57.

It is an important question, if arteritis temporalis can be said to be a clinically definable disease. The authors mentioned above seem to agree upon the peculiarity of the clinical picture. The onset, the symptomatology, the pathological anatomical findings and the good prognosis indicate a specific disease. As new reports have been published concerning this disease, it has, however, become more difficult to classify it as a separate disease of the temporal arteries. Symptoms from other vascular areas have frequently been observed. It is enough to mention the brain, the ear and aorta to point out some of the more important localisations where typical symptoms have appeared. There is also reason to ask, if the disease only affects arteries. Eckerström (1945) says that periphlebitis in the superficial temporal veins has been found in two patients with typical symptoms of arteritis temporalis. Both patients were 70 year old women and both of them had suffered from rheumatic symptoms. After a subacute onset with fever, tiredness, lack of appetite and above all a painful headache in the temples and the vertex. In each there appeared in the temporal regions reddened painful, nodular infiltrations corresponding with the position of the superficial temporal veins. In both cases the arteriae temporales were clearly palpable in front of the infiltrations and the temporal pulse was unmistakable. The author considered it to be a periphlebitis in the temporal veins. Otherwise nothing abnormal was found. Slight anaemia in one case, leucocytosis in both. BSR was high: 107 and 70 mm p h. respectively, and in one case still remained high after several weeks. In the other case it had fallen to 24 mm p. h.

after six weeks. Four to five weeks later both patients were afebrile and free from symptoms with the exception of a slight feeling of tiredness. Unfortunately no biopsy was made, but the author thinks it impossible that the palpated infiltration was indicated of arteritis temporalis. In 1946 Eekerström reported another case of periphlebitis temporalis which had a typical clinical picture of arteritis temporalis, in this case the diagnosis was verified by biopsy. Cooke, Cloake, Govan and Colbeck reported a similar case in 1946 but their diagnosis of phlebitis did not seem to be verified by biopsy and histological examination.

The etiology of arteritis temporalis is unknown. All attempts to isolate or incriminate pathogenic agents have so far been negative. The actinomycetic strain found by Horton is surely of no etiological importance. Tuberculosis and lues can also certainly be excluded.

The disease afflicts elderly persons exclusively, possibly women more than men. One 43 year old male patient is reported (Sjövall & Winblad) but only 5 out of 54 have been under 60 years of age and the average age of these 54 patients was 67 years. The onset is not very characteristic. No real prodromata are observed. In some cases there are symptoms from the upper respiratory tract, in others some rheumatic symptoms have preceded the disease. The patient feels very ill and very tired, most have a moderate fever and above all a headache, paroxysmal, intense and unrelieved by salicylates. It is located in the temples and on the vertex. The patient often describes it as a stabbing pain, sometimes even during the night. There is often hyperaesthesia of the scalp. Sleeplessness, night sweating, lack of appetite and loss of weight are often components of the clinical picture. Some time after the disease has started (from 2 weeks to 9 months) there appear local changes, which are of importance in the diagnosis. Such changes in the temporal arteries have given the disease its name. Possibly some difficulty in talking and opening the mouth have been observed a little earlier. The superficial branch of the temporal artery appears sinuous, swollen and reddened. The vessels often feels knotty, hardened and pulseless and is always very tender. Sometimes small knotlike formations can be palpated on the galea and over the mandibular joints. The changes in the vessels often disappear before the general symptoms and in some cases pulsations have been observed to reappear in the temporal arteries. On examination one can sometimes find general arterio-

sclerotic changes but in addition one can also find changes typical of arteritis temporalis in other vessels eg. the aorta, innominate carotid, subclavian, external jugular, radial, coronary, pulmonary, caeliac, mesenteric, renal, iliac, femoral arteries and in the central artery of the retina. Most interesting are two of the more unusual symptom groups; the cerebral and the visual groups. The former may consist of slight grades of mental impairment, but even stupor and coma may also present. The latter comprises symptoms from slight eye pain to dim vision, double vision, photophobia, reduced vision to total anopsia, ptosis, etc. In Andersen's survey, 24 cases of 57 are stated to have involved ocular symptoms. In at least 4 cases anopsia occurred. In such instances the clinical picture often becomes varying and confusing. Common to all known cases, however, are a moderate hypochromatic anaemia, slight leucocytosis, and usually a decidedly increased BSR, which remains high even after the patient has become afebrile and free from pain, which may take several months to a year. Splenomegally, hypertension, and albuminuria, which have been mentioned in a few cases, probably do not belong to the typical clinical picture. Further physical findings reveal the presence of roentgenological changes of the cervico-dorsal column (intervertebral osteochondrosis with spondylosis and spondylarthrosis) pointed out by Broch and Ytrehus. The connection between these changes and the arteritic changes seems, however, to be very debatable. But the authors point out that an obvious improvement in the condition of the patient occurred after X-ray treatment of the cervical column; consequently, a certain connection cannot simply be excluded.

No special complications seem to occur relative to arteritis temporalis, provided the cerebral and visual symptoms are not taken into consideration; this would not seem justified, however, since such symptoms are part of the syndrome and not complications. — The prognosis has always been considered wholly good, a fact which some authors (Horton and Magath) have regarded as a reason against viewing arteritis temporalis as a separate variation of periarteritis nodosa with its usually poor prognosis. The majority of the cases of arteritis temporalis have on the whole definitively recovered. Relapses have been described, however, by, among others, Broch and Ytrehus. Lately, it has become apparent that the prognosis is not so completely favorable as was formerly believed. Cooke reports in 1946 that out of

his 7 patients 3 died whilst one regained full health. Andersen states in 1946 that out of 57 known cases 7 were fatal, in each case death was closely connected with this disease. In 4 cases the cause was cerebral vascular complications, in 2 cases coronary sclerosis or occlusion and in one case pulmonary haemorrhage. In the latter case there was a question of arteritic changes in the pulmonary arteries. Unfortunately, no histological examination was made. What Horton and Magath originally meant by arteritis temporalis has more and more proved to be an element of a general arterial disease, and consequently, there is reason to consider the prognosis uncertain for the present.

No infallible therapy has as yet been devised. Horton and Magath point out that potassium iodide and large doses of neoarsphenamine have been tried but with no decided effect. Besides purely symptomatic therapy, vitamins, sulphur compounds and penicillin have been used, the latter because of the benign sepsis character of the disease, but with no apparent result — not even as regards the febrile condition. Oldberg tried short-wave treatment locally, and Broch and Ytrehus have administered X-ray therapy and report some effect. It is remarkable that after biopsy in artery temporalis the local symptoms (headache) in many cases disappeared. The part played by the severing of the sympathetic fibres in this connection is far from clear. But in most cases the patients have recovered spontaneously regardless of therapy, and, consequently it is very hazardous to estimate its effect.

Pathological-Anatomical Changes.

Horton and Magath state that arteritis temporalis begins as a periarteritis. The process either ceases at this point or continues, affecting the media and the intima and resulting in thrombosis in the lumen. There are certain regions with granulomatous tissue in the adventitia, where an infiltration of round cells around the vasa vasorum may also be found. In certain cases the media is necrosed and replaced by granulation tissue with numerous giant cells. The intima is greatly thickened and has an acellular basal stratum. This proliferation of the intima seems to have advanced by degrees. Aneurysms are never seen. In this connection it should be of interest to study the findings described by Post and Sanders regarding the eye grounds in arteritis temporalis.

There is no periarteritis, nor any other tissue changes which might have been expected had it been a case of acute inflammation. The findings indicated chiefly a degenerative process. But at intervals there were small haemorrhagic extravasations and a more substantial haemorrhage, which was suggestive of an infarct. The central artery of the retina was occluded and, in conjunction with the minor local haemorrhages in the surrounding region, the condition was reminiscent of arteriosclerosis. The authors cautiously turn their assertion around and state the possibility that certain changes in the fundus, described as due to arteriosclerosis, might constitute degenerative conditions, similar to those of arteritis temporalis. These would later pass through a localized inflammatory phase, as happens in the temporal arteries. The differential diagnosis, before the characteristic changes in the temporal vessels have developed, is very difficult. At the beginning, the picture is reminiscent of a sepsis with fever, general discomfort, lack of appetite, loss of weight, leucocytosis, and a high BSR. When headache has set in, sinusitis, migraine, histamine headache, arthritis, myosis, neuralgia, tumours, and meningitis must, among other things, be eliminated, and in most cases this probably does not cause any great difficulties. But to isolate the disease from a number of other vascular diseases is considerably more difficult. Periarteritis nodosa, thromboangitis obliterans, and rheumatic arteritis should receive first consideration.

Kussmaul and Mayer as early as 1866 presented the symptoms of periarteritis nodosa, which could be briefly summed up as follows: fever, fatigue, loss of weight, pains in the joints, muscles, and viscera, slight leucocytosis, and anaemia; the course of the disease having the characteristics of sepsis. There has been some divergence of opinion as to the histological process. Von Albertini maintains that in the case of periarteritis nodosa the inflammation begins in the intima although it rapidly passes to the media contrary to the periarteritic beginning of arteritis temporalis. In connection with periarteritis nodosa, proliferations are formed in the intima and the lumen is frequently thrombosed, and every now and then aneurysms and necrosis are present in the media. This process, which also applies to inflammation of the adventitia, produces nodules in the vascular walls, these nodules contain mononuclear cells, leucocytes with polymorphous nuclei, and eosinophil cells. Giant cells are never seen (according

to Horton and Magath). The affected vessels are principally the small arteries of 3—5 mm diameter. The prognosis for periarteritis nodosa has formerly been considered to be decidedly unfavorable. Recently several authors have reported that the disease may take a form a more favorable course.

What keeps arteritis temporalis apart from periarteritis nodosa from the histological point of view is, above all, the fact that the former never exhibits aneurysms of the walls, nor is it associated with eosinophil cells. Jennings maintains, however, that a distinction between arteritis temporalis and periarteritis nodosa, which cannot possibly be made on a clinical basis, is very difficult to achieve also on a pathological-anatomical basis. He asserts that the chronically productive arteritis of arteritis temporalis begins in the media and that it might be a variation of periarteritis nodosa.

The position of arteritis temporalis in relation to rheumatic arteritis has also been the subject of much discussion. Due to the analogous progress in the initial stages in some cases of rheumatic diseases and arteritis temporalis, attempts have been made to relate the latter disease to or even to regard it as a component part of rheumatic disease. The microscopic aspects, however, do not always agree for the two conditions. According to Klinge, it is mainly the intima that is affected by rheumatic arteritis, while the media and the adventitia may be almost intact. Harbitz reports that he has found rheumatic arteritic changes in the ascending aorta as well as in the innominate artery, and describes microscopic findings of infiltrations in the adventitia, the media, or in the connective tissue surrounding the outgoing arteries. These infiltrations contain chiefly lymphocytes and large mononuclear cells, sometimes also polynuclear cells, occasionally arranged in nodules. In the intima there were simultaneously cushion-like areas of hyperplasia and degenerative sites. Harbitz considers this type of inflammation to be a separate form microscopically and analogous to the inflammation of the myocardium and to that of the joints when the rheumatic disease is present.

If the clinical aspect of arteritis temporalis is to a certain extent similar to that of periarteritis nodosa, then the difference is very much greater when arteritis temporalis is compared with thromboangitis obliterans. The clinical findings are in poor agreement. This is also the case where cerebral symptoms have been

present in the latter disease, which does not seem to be particularly rare. Hausner and Allen among others have reported on 14 cases from the Mayo Clinic and Antoni on a few cases from Stockholm. The microscopic aspects have had a typical Bürger character, it has been stated. Viewed from the pathological-anatomical aspect, the difference between the two diseases has been less. von Albertini believes that an inflammatory initial stage, approximating to the concept of «phlebitis migrans», first develops in the case of endangitis obliterans (thromboangitis obliterans). This inflammatory process, which is a fibrinous inflammation of the arterial intima, is distinctly localised and of short duration, leaving a defective endothelium. Secondly a productive reaction sets in resembling in certain aspects tuberculoid granulation tissue, this grows into the fibrin pulp and becomes fibrinoid, it is then converted into hyaline tissue. Already in the early stages, the proliferating cells break through the elastica interna and more or less destroy it. The final scar stage of thromboangitis obliterans is gradually calcified. — A dissenting opinion has been advanced by Gruber and Rieder, who claim that hyperplasia of the intima is primary, whilst the inflammatory vascular changes are secondary phenomena and consequently a result of the gangrene. Other authors, however, consider the inflammation to be a result of an allergie-hyperergie reaction of the vascular system. (Jaeger, Hueck, etc.), a theory which has been used by certain investigators in order to explain many different vascular diseases. Ebrström, in his studies on diffuse glomerulonephritis, periarteritis nodosa, and rheumatic arteritis, mentions vascular changes as the result of the administration of antigen, which has mainly consisted of the bacterial products of hemolytic streptococci. Rintelen's attempts to produce an allergie-hyperergie arteritis experimentally by sensitizing rabbits with injections of swine serum and nonhaemolytic streptococci into the carotid artery are interesting in this connection. The vascular reaction achieved was distinctly inflammatory: the vascular wall was infiltrated by cells, and the elastic elements were torn or had disappeared. The intima and the interior strata of the media were necrosed and the lumen was filled with necrotic debris or thrombi. A histological picture typical of arteritis temporalis was evidently never obtained. Jaeger's section findings in the course of his tests on animals are quite remarkable. He found that arteries of different size reacted in a different manner after

exposure to the same infectious or toxic agents. The major arteries responded with a condition similar to that of recurrent thrombendarteritis, the medium-sized arteries showed fibrin thrombosis and giant cellular organization tissue, and the minor arteries exhibited a condition similar to that of periarteritis nodosa.

Professor Bergstrand emphasizes similarly the prevalence and significance of the allergic vascular changes. »With allergic inflammation the vessels, both arteries and veins, as well as capillaries, often exhibit great changes . . . These vessel changes, which were observed as early as 1866, were long apprehended as a special disease and went under the name of »periarteritis nodosa». As has been mentioned above, they are in reality only a part symptom of the allergic inflammation and are therefore met with in a considerable number of allergic diseases . . .»

Since the opinions as to the origin of the different vascular diseases vary considerably, it is quite natural that no uniform classification of these diseases has been agreed upon. It may, consequently, seem to be a precarious matter to further enrich the nomenclature with more or less carefully defined syndromes. But since both the symptomatology and the pathological-anatomical aspect of arteritis temporalis in part deviate from those of all the arterial diseases referred to above, it might for practical reasons be suitable to separate arteritis temporalis for the time being, clinically and pathologically, as a specific disease. It is then essential to keep in mind that the changes in arteritis temporalis only produce the local symptoms of a general disease.

Summary.

Two cases of the Arteritis Temporalis Syndroma are reported. In both cases the subjective and objective findings are characteristic. Both are now (July 1947) free from symptoms. The disease is discussed with special references to allergic diseases in the arteries. The opinion that the changes of the temporal arteries are only a local symptom of a general artery disease has been proved.

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A Case of Refractory Anemia in a Final Stadium, Suggestive of Aplastic Anemia With Increased Pigmentation of the Skin, Successfully Treated With Folic Acid.

By

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Our knowledge of hematology does not so far permit an indisputable classification of the blood diseases. Consequently, the nomenclature referring to these conditions has become confusing and the reports, appearing in rapid succession in different quarters regarding the effect of folic acid on various blood diseases, are at times misleading. All hematologists do not, for instance, mean the same phenomenon when speaking of aplastic anemia. In several publications concerning the indications for folic acid it is stated, from a general point of view, that this substance is without effect on aplastic anemia, the authors neglecting at the same time to specify their conception of this term. Such a generalization must of course be regretted. The following attempt at a definition, quoted from a work by Bomford and Rhoads (1940), may be presented as an acceptable description in a practical sense: "The essential feature is a reduction in the amount of hemopoietic marrow below the normal for the patient's age (Turnbull 1934, 1936). The blood picture shows a decrease of erythrocytes, granular leucocytes and platelets, with erythrocytes, normal in size and shape, and with an absence both of signs of regeneration and of immature cells in the blood. The condition

has usually been described as a relatively acute one, almost confined to children and young adults, and characterized by severe anemia and hemorrhages." If this definition is accepted, the number of definite cases will become fairly small and the majority of investigators are, no doubt, willing to testify to the inactivity of folic acid in cases of this type. I shall continue to quote Bomford and Rhoads, as follows: "More recent accounts have shown that the disease may occur at other ages, that it may have a more variable course than was previously recognized, and that the presence in the blood of slight macrocytosis, of immature red and white cells in small numbers, and of an increased percentage of reticulocytes is compatible with the existence of a severely hypoplastic marrow at autopsy. The term 'a plastic anemia' can reasonably be used to include any anemia in which there is definite hypoplasia of the hemopoietic marrow." It will have to be taken into account, on the basis of this wide definition of such a heterogeneous group, that a variety of anemic conditions may be encountered. Bomford and Rhoads performed some excellent work in bringing order into this confusion by compiling a series of different anemic groups into one, called refractory anemia. This group is characterized by a mutual, combining factor, viz. failure of the anemias to respond to any known treatment. Future research will show to what extent individual anemic forms belonging to this group are affected by folic acid. However, it is quite certain that several cases in the group of refractory anemia, during some stage of their existence, fulfilled the above stipulated criteria regarding aplastic anemia. It is, furthermore, well known that practically any form of anemia can be burned down and end up in a final stadium which is impossible to distinguish from the aplastic anemia. This occasionally happened in the case of pernicious anemia before the liver therapy was introduced. Still, even in this aplastic stadium, the anemia responded to the liver therapy. An analogous condition is conceivable also with folic acid.

Recently, at the forementioned medical department, a case of anemia was observed which seemed to be an illustration of these arguments. It began with a picture of a hyperchromic, macrocytary anemia of the refractory type. Finally, after a course of several years, it reached a stadium where it was impossible to distinguish it from aplastic anemia. It responded at this stadium to treatment with folic acid.

An account of the case. The patient is a man, aged 64, who has lived all his life in the country where he has managed his own farm. He has spent much of his time out of doors, but lacks known exposition to toxins, had no *abusus ethyli seu nicotini*, no dietetic anamnesis speaking in favour of a deficiency disease of some kind. His father had died of an unknown blood disease. Otherwise, nothing was discovered in support of the assumption of a hereditary influence. An examination of one daughter and a brother of the patient's did not reveal a blood disease. Tuberculosis occurs in the family as well as symptoms of peripheral vascular diseases (Raynaud's disease or allied conditions).

He had had erythema nodosum in connection with rheumatic fever as a child. He has suffered a number of periods of insomnia and nervousness. He was, during such a period in 1906-07, remarkably pale but his blood was not subjected to examination.

The onset of his blood disease cannot be definitely dated. However, ever since 1939, he has felt tired, has been conspicuously pale, has suffered from insomnia, and nervousness, has been troubled by shortness of breath and palpitations which increased at exertion during which he has also felt symptoms resembling angina pectoris. He had no digestive disturbances, nor loss of weight.

The diagnosis was a hyperchromic, macrocytary refractory anemia with mature cellular marrow. At the Easter of 1944, anemia was diagnosed for the first time. An anemia of the hyperchromic type was ascertained in connection with his admission to a hospital owing to a benign and rapidly transient ischias. Blood count on admission: hemoglobin 53 per cent, red cells 2,300,000 per ml., colour index 1.15, white cells 3,300 per ml. Differential count: lymphocytes and monocytes together 90 per cent. When the anemia failed to yield to any treatment except transfusions of blood, he was transmitted to the Central Hospital for special examination, where I saw him for the first time in July 1944. He was a tall, strongly built man with a pale complexion and pale mucous membranes, but without any signs of glossitis and his tongue was perfectly normal. In the axillae and groins, a few hard and easily displaceable lymphatic glands were palpated, ranging from small ones up to the maximum size of a pea or bean. These have not changed in size or in consistency during the course of the years. Otherwise, the somatic examination did not reveal anything of interest. Free HCl was found in the ventricle. He had considerable anemia of the hyperchromic type, hemoglobin 45-50 per cent, red cells 1,700,000-2,000,000 per ml and white cells 3,000-6,000 per ml. Colour index lay all the time above 1.0, mostly around 1.4, thrombocytes 150,000 per ml. The sedimentation rate varied between 25-50 mm/l hour. In the peripheral blood, a lymphocytosis of approximately 50-60 per cent, moderately pronounced aniso-, poikilo- and macrocytosis. The sternal marrow was rich in cells with lively erythro- as well as myelopoiesis, both of which seemed to be normally differentiated. No megakaryoblast marrow. He was treated with Heptomin injections, iron medication per os and different vitamin preparations, all to no effect. Blood transfusions produced transient improvement of the blood. A series of

examinations was performed, all of which turned out negative, among them a series of röntgenographic examinations of, inter alia, the lungs, the heart, the skeleton, the digestive canal, electrocardiography, analyses of the feces, diastatic determinations of the urine, worm egg analyses of the feces. At the Röntgen examination, the only positive finding was considered to be a slight enlargement of the pancreas (the distance between the vertebral column and the duodenal sweep exceeding the breadth of one vertebra, this distance having been seen at repeated Röntgen controls during 1944—1947 to vary between the breadth of 1—2 vertebrae). For this reason, we at first discussed the possibility of a pancreatic cancer with metastases of the bone marrow. However, the course of the disease completely eliminated this suspicion.

In September, 1944, the patient was transmitted to our Medical Department where we have for almost three years been able to follow the course of his blood disease. No change in the somatic condition has occurred. A neurological examination gave no signs of subacute, combined degeneration of the spinal cord. The spleen was not palpable but slightly enlarged in the röntgenogram. Normal fasting blood sugar. Wassermann reaction negative in the blood. Hemoglobin varied during his stay of one month at the hospital between 50—60 per cent, corresponding to a red cell value of 2,000,000—2,500,000 per ml. Colour index above 1, mostly at about 1.4. White cells approximated to 4,500 per ml. with 64 per cent lymphocytes and 9 per cent monocytes. Thrombocytes equalled 110,000 per ml. Reticulocytes 9—12—16 per mille. High serum iron, 0.200—0.230 mg%. No increased fragility of the red corpuscles: beginning hemolysis at 0.44 per cent, total hemolysis at 0.32 per cent. The sternal marrow was exceedingly rich in cells with all cells characteristic of the marrow represented in it. The red series was strongly hyperplastic, in relation to the white series, with a ratio of erythro-myelopoiesis of 1:1. All the stages of the red series were well represented and the maturation seemed to take place fairly normally with occasional nuclear buds. No megaloblasts. Abundance of mitoses. The white series was normal with slightly increased amount of mitoses. Megakaryocytes of the normal type. (I wish to thank S. Roland-Franzén, medical student, for valuable help in analysing this and the following sternal punctates.) The patient was treated with Heptomin injections without any effect and was discharged without improvement. Re-admitted in the middle of March, 1945.

Unchanged somatic condition. The Röntgen examination this time gave no indications of a pancreatic enlargement. Functional test of the liver: Hippuric acid test 54 per cent, urine urobilin +, Hijman's v. d. Bergh dir. neg., indir. +, bilirubin content of the blood 1.6 mg%, icteric index (Meulengracht) 1/12, blood phosphatase determination 7 units, serum citric acid 14 γ /ml, the Takata-Ara reaction: no flocculation in tubes. Blood: hemoglobin between 45—59 per cent, red cells approx. 2,000,000 per ml, colour index 1.2—1.3, white cells 3,000—4,000 per ml, thrombocytes gave varying values 50,000—70,000—130,000—200,000 per ml, reticulocytes about 10 per mille. Sternal marrow: white series displaced to the left but otherwise normal.

Red series normal from a quantitative point of view but not from a morphological one. The reticulum strongly hyperplastic. The following distribution was obtained per 1,000 counted cells: myeloblasts 0.5 per cent, promyelocytes 6.3 per cent, myelocytes 12.3 per cent, metamyelocytes 15.1 per cent, stab-nuclear leucocytes 18.5 per cent, segment-nuclear leucocytes 5.7 per cent, eosinophile leucocytes 0.8 per cent, basophile leucocytes 0 per cent, lymphocytes 4.5 per cent, monocytes 0 per cent, proerythroblasts 1.6 per cent, basophile normoblasts 5.7 per cent, polychromates 13.6 per cent, orthochromates 2.5 per cent, reticular cells: lymphoids 12.8 per cent, plasma cellular 0.1 per cent, phagocytizing 0 per cent. Isolated megakaryocytes, isolated Jolly bodies, mitoses fairly common in the red series. The polychromates often showed nuclear budding and basophile punctation. Erythro-myelopoietic ratio 1 : 3. Differential count of the peripheral blood: myelocytes 0.5 per cent, metamyelocytes 1.0 per cent, stab-nuclear leucocytes 24.5 per cent, segment-nuclear leucocytes 22.5 per cent, eosinophile leucocytes 1.5 per cent, basophile leucocytes 1.0 per cent, lymphocytes 34 per cent, monocytes and those resembling monocytes 15 per cent, Red blood corpuscle picture disclosed marked increase of anisocytosis, slight poikilocytosis and polychromasia. Strong anisocytosis among the thrombocytes, giant forms being usual.

He was treated with Heptomin injections, iron medication per os and nine blood transfusions. After some of these transfusions he was troubled by chills and fever. The treatment did not give any increase of the reticulocytes. However, the blood values improved from the blood transfusions and he was discharged with a hemoglobin value of 87 per cent and red cell count of 4,400,000 per ml.

After his discharge, the blood values were maintained for some time. However, after a month, the anemia became pronounced and he was given a new blood transfusion. Notwithstanding the fact that the patient was given nine blood transfusions, during the next five months, the hemoglobin value did not exceed 50 per cent. The patient began, moreover, to be increasingly inconvenienced by fatigue, shortness of breath and palpitations. In October, 1945, he was re-admitted to the department. Somatic state unchanged. Hemoglobin value varied between 50—60 per cent, red cells 2,000,000—2,500,000 per ml. Colour index lay on an average lower than during his previous stay at the hospital, now being approximately 1.0—1.3. White cells varied from 1,800 to 3,000 per ml., thrombocytes 98,000 per ml., reticulocytes 6—10 per mille. Differential count of the peripheral blood: stab nuclear leucocytes 10 per cent, segment-nuclear leucocytes 20 per cent, eosinophile leucocytes 2 per cent, basophile leucocytes 0 per cent, monocytes 13 per cent, lymphocytes 55 per cent, marked increase of anisocytosis and poikilocytosis. Blood corpuscle measurement: 8.5 per cent = 7.2 my, 8.1 per cent = 7.3 my, 57 per cent = 8.4 my, 8 per cent = 9 my, 17 per cent = 9.6 my, 1.5 per cent = 10.2 my. Sternal marrow: myeloblasts 0.75 per cent, promyelocytes 9 per cent, myelocytes 13.75 per cent, metamyelocytes 24.5 per cent, stab-nuclear leucocytes 20.25 per cent, segment-nuclear leucocytes 9 per cent, eosinophile leucocytes

0.25 per cent, basophile leucocytes 0 per cent, lymphocytes 2.5 per cent, monocytes 0 per cent, plasma cells 0 per cent, lymphoid reticulum cells 9.25 per cent, phagocytizing reticulum cells 0.25 per cent, proerythroblasts 0 per cent, pronormoblasts 0.25 per cent, basophile normoblasts 5 per cent, polychromatic normoblasts 8.5 per cent, orthochromatic normoblasts 0.25 per cent. The red marrow, accordingly, began to show signs of being forced back at the expense of the white marrow. Serum iron 0.201 mg%, a resistance determination of the red cells not disclosing any signs of increased fragility. Functional test of the liver: Hippuric acid test 44 per cent (undoubtedly misleading as in previous test when inadequate urinary samples were obtained, the patient had mild prostatic symptoms), urine urobilin ++. Hijman's v. d. Bergh dir. neg., indir. pos. icteric index (Meulengracht) 1/9, blood phosphatase determination 10 units, serum citric acid 15 y/ml. Takata-Ara reaction: no flocculation in tubes. A later icteric index (Meulengracht) 1/16. He was treated with Heptomin injections, penicillin for a period of ten days, 100,000 Oxford units daily, 15 blood transfusions. Even this time, he was observed to have a rapidly transient reaction after the blood transfusions in the form of chills and a rise in temperature. The spleen was seen to be slightly enlarged in the röntgenograms. No worm eggs in the feces. Discharged after nine weeks of treatment with hemoglobin 80 per cent, red cells 3,800,000 per ml.

The anemia passes into an aplastic stadium and skin pigmentations appear. During the following years up to October of the year 1946 when the patient was re-admitted to the department, he stayed at his home and was given repeated blood transfusions at a hospital in the proximity. Asked about a later skin change, he stated that the skin had assumed a slightly darker shade since the turn of the year 1945—1946. This change in the skin was, however, inconspicuous enough to be laconically reported, at our physical examination at his admission to the Hospital in October, 1946, as "pale colour of the skin". My definite impression is that this change in the colour of the skin did not appear until in December of 1946, when it, on the other hand, in very short time reached a high degree of intensity. The examination comprised, as usual, careful Röntgen examinations and the findings were found to be the same as previously, i. e. a slight splenic enlargement, liver of normal size, some glands in the axillae and the groins ranging up to the maximum size of beans, free HCl in the ventricle. The anemia was more pronounced than earlier and the colour index had been displaced further downwards resulting in a no longer hyperchromic but ortho-hypochromic anemia. Hemoglobin approx. 30 per cent, red cells 1,500,000 per ml, white cells 1,700—3,000 per ml. Colour index varied between 0.85—1.0. Thrombocytes 22,000—90,000 per ml. Sternal marrow still rich in cells but at the expense of the erythropoiesis which was markedly reduced, causing the ratio of erythromyelopoiesis to be 1 : 32. Thus, the myelopoiesis predominated entirely and mainly consisted of metamyelocytes and stab-nuclear leucocytes, whereas the segment-nuclear leucocytes were very sparse. The nuclei showed signs of pyknosis and segmentation seemed to be checked.

The erythropoiesis was strongly forced back and injured. Hyperplastic reticulum. Plasma cells and megakaryocytes occurred. Diagnosis: Total medullary damage. Reticulocytes 2—4—9 per mille.

The patient's blood disease had now entered an aplastic, final stadium with erythropenia, leucopenia and thrombopenia. The prognosis seemed extremely unfavourable. He had, in the course of the years, been given about seventy blood transfusions with only transient effect. Iron therapy, liver extract injections, various vitamin infusions, all had failed to help. We began a new series of blood transfusions. In spite of the administration of 350 ml of blood every other day, the hemoglobin value only exceptionally exceeded 50 per cent, being mostly approximately 30 per cent. He belonged to the blood group O MN RH (+) and was given such blood but, notwithstanding conformity to blood group, was at times subjected to severe, shock-like symptoms in direct connection with the transfusions, with chills and a rise in temperature to about 104° Fahrenheit. The blood values often fell rapidly in connection with such a transfusion which had taken place with subsequent complications. We obtained the distinct impression that the administered blood was hemolyzed. However, pains in the lumbar region did not form part of the complication picture, nor did hematuria. In the beginning of December, we were struck by the forementioned dark-pigmentation of the skin. This rapidly became pronounced and entirely concealed the earlier anemic pallor of the skin. The skin changes greatly resembled, as regards appearance and localization, those manifested at Addison's disease. They were most marked in the face, on the neck, on the backs of the hands, penis and scrotum. The colour varied from deep amber to chestnut brown. The pigmentation was pronounced on the elbows in connection with a dry and rough skin not unlike the changes manifested at pellagra. However, other symptoms indicative of pellagra were lacking, no digestive disturbances apart from an obstipation, no mental changes. In addition, the patient had been given large quantities of different vitamins, B-vitamins not least. He had been administered for the last month daily injections of Becozymes containing the whole B-complex, as well as nicotin-acid-amide. An attempt to give daily injections of 1.2 grammes of nicotinic acid amide only for twelve days failed to cause a reduction in the pigmentation. On the contrary, it increased in intensity during this process. The possibility of Addison's disease was considered. However, several factors argued against this diagnosis, e.g., inter alia, the absence of asthenia over and above the degree of anemia, anorexia, hypotonia, decrease in the serum sodium and chlorides, elevation of serum potassium, blood urea and non-protein nitrogen. An attempt was also made with sublingual administration of desoxycorticosterone without effect. No porphyrinuria. The possibility of hemochromatosis will be discussed below.

Favourable effect of folic acid in an aplastic stadium. The general condition of the patient was now bad, the anemia was pronounced in spite of the blood transfusions, the values being mostly about 34 per cent for hemoglobin, 1,800,000 per ml for red cells, the white cells

varying between 400—800—1,000 per ml. On a few, isolated days, however, high values were noted, partly relating to the time interval from the preceding blood transfusion which was free from complications, partly also because of the different blood investigators employed. Thus, certain blood counts were made by medical students. This was the case with the remarkably high blood values obtained on the same day folic acid was introduced, hemoglobin 58 per cent, red cells 3,000,000 per ml, these values being undoubtedly too high considering the still extremely bad general condition of the patient at the time and the earlier fairly constant low values. After this day, an experienced, hematologically trained, laboratory nurse, performed all the blood counts of this patient. On account of the exceedingly scarce supply of folic acid in the country at the time, this substance had not been put to the test earlier in this particular case. Now in January 1947, folic acid was introduced in the therapy in daily doses of 0.125 grammes. This dose could be increased after a month to 0.151 grammes. The effect of this therapy was rapid and striking. His general condition improved greatly during the very first week, during which time also the reticulocytes increased from the earlier, fairly constant values of 2—3—6 per mille to 70 per mille. The transfusions given every other day could be discontinued. After a week, the blood values were as follows: hemoglobin 67 per cent, red cells 3,100,000 per ml, white cells 3,500 per ml. After treatment for a good fortnight, the corresponding values were 87 per cent, 4,700,000 and 3,900 per ml, respectively. In connection with an infection resembling influenza, the blood values were slightly reduced, having since remained at approximately the following figures: hemoglobin 80 per cent and red cells 4,000,000 per ml. This metamorphosis could also be distinctly followed in the sternal marrow. The earlier, strongly reduced erythropoiesis returned and the erythro-myelopoietic ratio was normalized from the previous 1:32 to 1:4—5. The myelopoiesis was moderately displaced to the left. Typical segment-nuclear leucocytes were rare. The erythropoiesis was relatively severely injured with basophile punctating and occasional nuclear budding. Plasma cells and megakaryocytes were normal. The reticulum moderately hyperplastic. Thrombopenia (values of 25.00 to 35,000 per ml) as well as a relative lymphocytosis in the peripheral blood of approximately 50—60 per cent remained unchanged after the treatment. It is noteworthy that also the skin changes decreased in intensity to some extent soon after the introduction of the folic acid treatment. After desquamation, the skin grew paler. An earlier, constant obstipation rapidly disappeared.

The patient was discharged from the hospital and has since at home taken daily doses of 0.035 grammes of folic acid. His general condition has all the time been satisfactory. Sometimes he felt tired and nervous, but it should be borne in mind that he has throughout his life looked stronger than he felt. Hemoglobin value equalled approximately 88 per cent, red cells about 4,000,000—4,300,000 per ml, white cells 5,600—11,600 per ml. He was re-admitted for control examination in the middle of March, 1947. He had for the last month been troubled

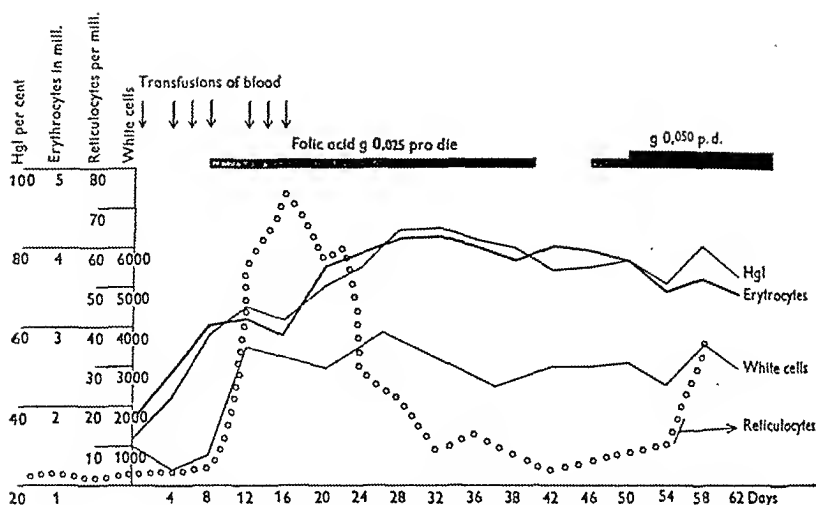


Fig. 1. The response of the blood to folic acid.

by frequent impulses to urinate, which were regarded as due to a moderately pronounced prostatic hypertrophy. At admission, he had an infection of the urinary tract which was quickly cured by penicillin. He looked healthy but still had clearly increased pigmentation of the skin with the same localisation as previously. The pigmentation was particularly marked on the penis and scrotum. During his stay at the hospital, the pigmentation increased further in places exposed to the rays of the sun which was attributed to added exposure to the sun. Blood values at admission: hemoglobin 85 per cent, red cells 4,050,000 per ml, colour index 1.04, white cells 5,100 per ml, thrombocytes 36,500 per ml, reticulocytes 13 per mille. Differential count of the peripheral blood: metamyelocytes 0.5 per cent, stab-nuclear leucocytes 4.5 per cent, segment-nuclear leucocytes 17.5 per cent, eosinophile leucocytes 1.5 per cent, basophile leucocytes 0 per cent, lymphocytes 72.5 per cent, monocytes 3.5 per cent. Red blood corpuscle picture was characterized by an increased anisocytosis with tendency towards macrocytosis. Serum iron 0.071 mg %. In spite of the considerable thrombopenia, no signs of increased tendency towards bleeding. Normal bleeding and coagulation times. Hess Test: no petechiae. No increased fragility of the red corpuscles with beginning hemolysis at 0.42 per cent and total hemolysis at 0.34 per cent of sodium chloride. Blood cholesterin 165 mg %, normal fasting blood sugar. Functional liver test: Hippuric acid test 109 per cent, urobilinuria +, Hijman's v. d. Bergh dir. and indir. neg. Icteric index (Meulengracht) 1/4, blood alkaline phosphatase determination 8 units, Takata-Ara: flocculation in 2 tubes. Thymol turbidity test: 5.5 units. Sternal marrow: erythropoiesis still forced back at expense of a principally metamyelocytary to stab-nuclear myelopoiesis. Ratio of erythro-myelopoiesis 1:10. Erythropoiesis is mainly represented by polychro-

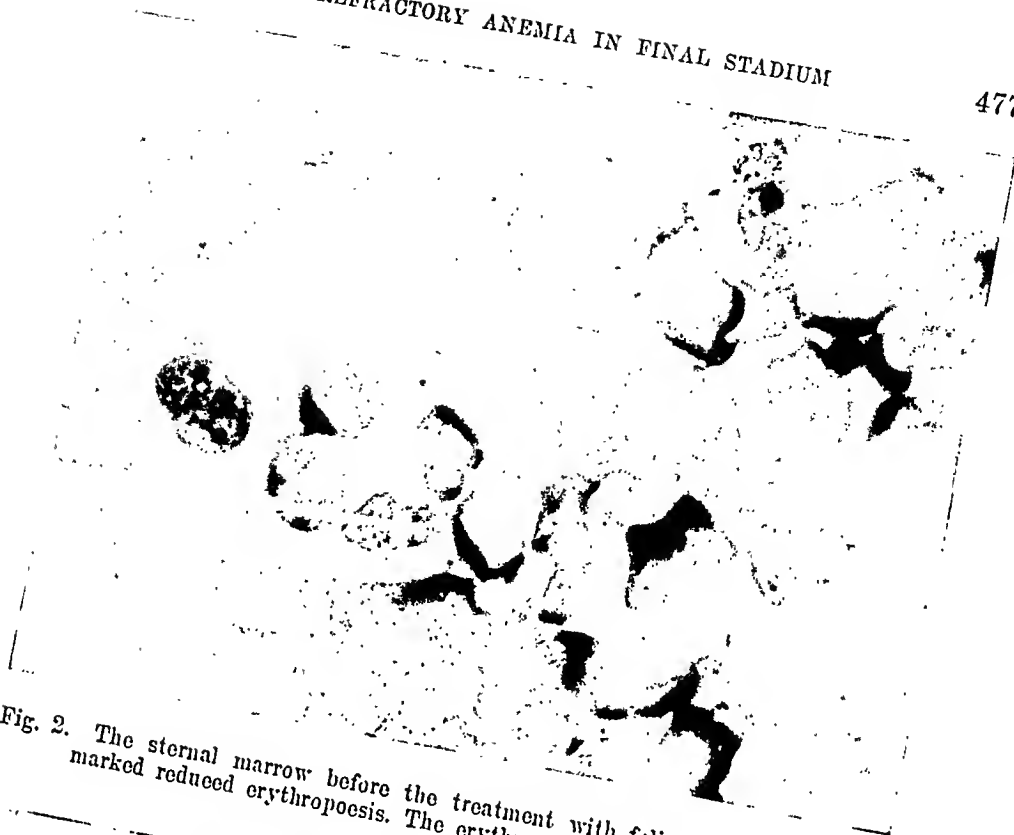


Fig. 2. The sternal marrow before the treatment with folic acid, showing the marked reduced erythropoiesis. The erythro-myelopoietic ratio 1:32.

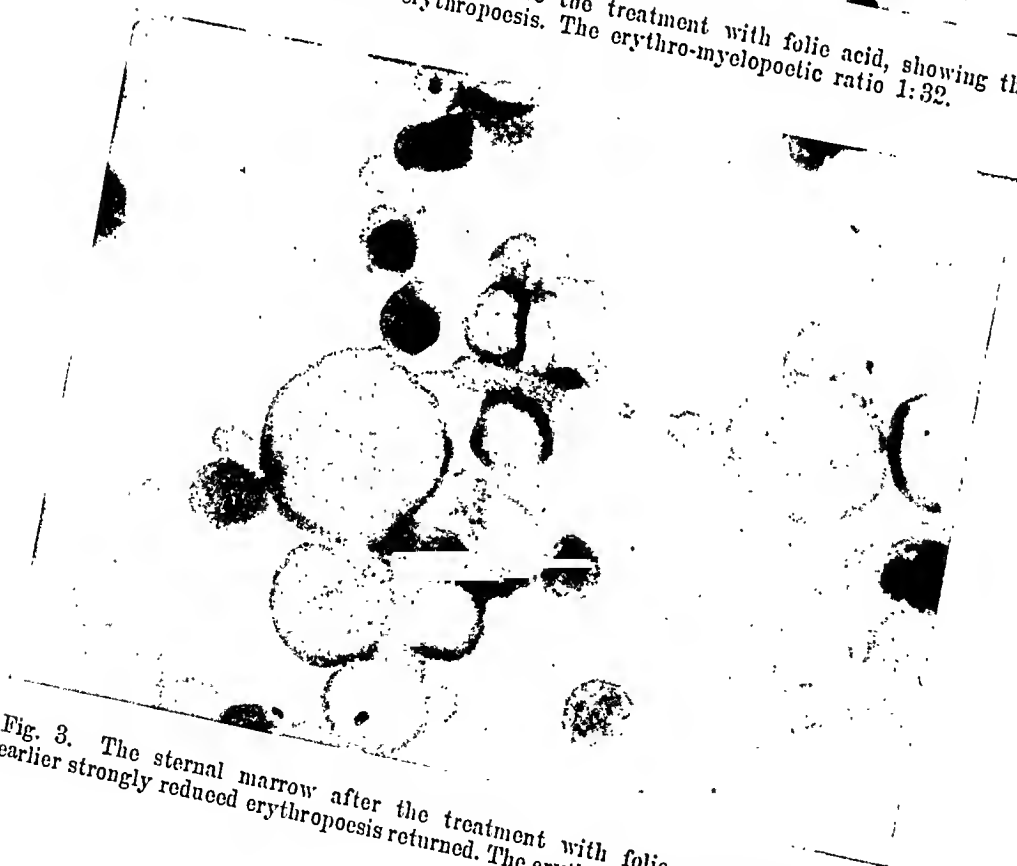


Fig. 3. The sternal marrow after the treatment with folic acid showing the earlier strongly reduced erythropoiesis returned. The erythro-myelopoietic ratio 1:4-5.

mates, partly degenerative. Thus, the marrow gives the impression of no longer responding quite satisfactorily to folic acid which, moreover, cannot be said to have cured him of his blood disease. Still, he was fit for work and free from symptoms and this must be considered a fine result in view of his deplorable condition at the commencement of this therapy.

Discussion.

As was pointed out in the introduction, this anemia was interpreted, in accordance with the terminology used by Bomford and Rhoads, as a case of refractory anemia with partly mature cellular marrow or pseudoaplastic anemia. These authors classified the refractory anemias into four different groups, at the same time strongly emphasizing the fact that the groups were not sharply defined, that intermediary forms exist and, further, that cases ascribed to one of these groups at the biopsy examination were found at autopsy to have changes in the marrow more indicative of another group. Apparently, the anemias may in certain cases pass through several group stages. The group of refractory anemia with partly mature cellular marrow is characterized by the following more constant changes in the marrow, apart from what is evident from its name; the proportion of erythropoietic to leucopoietic cells increased above the normal and the proportion of immature erythropoietic cells to normoblasts increased greatly. In the continued course, the anemia in the present case was, however, distinguished by the fact that erythropoiesis was increasingly forced back at the expense of the myelopoiesis. It, therefore, seems difficult to make it conform with Bomford and Rhoads' classification, considering that it did not represent a typical case belonging to the group of refractory anemia with hypocellular marrow, nor to that of refractory anemia with immature cellular marrow. This is, in fact, most simply explained as an anemia finally burned down to an aplastic anemia with erythropenia, leucopenia and thrombopenia.

The patient was throughout in surprisingly good condition, even when the anemia was at its peak which entirely conforms with the general aspect of anemias of this kind. Since Bomford and Rhoads, in a remarkably large number of their cases of anemia, were able to ascertain in the patients' exposure to potentially toxic substances, a careful analysis was performed in our case without affording any indications for such an etiology.

When estimating the result of folic acid treatment, the possibility of a spontaneous remission should be considered. Undoubtedly this is more frequent than was earlier believed. In the present case, the course would not render this likely.

Skin changes of the type increased pigmentation are far from uncommon in the case of refractory anemia. Bomford and Rhoads, in their comprehensive material of 66 cases, reported skin changes in no less than 12, being most frequent in the group of partly mature cellular marrow. Autopsy in the majority of these cases showed signs of a general hemochromatosis in various organs. However, only one of these cases disclosed simultaneous diabetes mellitus. The skin changes in their cases were identical with ours as regards appearance and localization. Similar changes have been described in a number of publications by, among others, Dacie, Leewen, Uehlinger, Hjorth regarding cases of refractory anemia of the Fanconi type, and in one case of so-called aplastic anemia by Hurst and Kark (treated with 290 blood transfusions) and by Jequier-Doge, and others. We are, accordingly, most inclined to interpret the pigmentation in our own case as connected with a hemochromatosis. The microscopical examination did not disclose hemosiderin but only an increased melanin content in the skin, nor did the intradermal test with potassium ferrocyanide acc. Fishback, blood sugar series and glycogen tolerance curves give any indications of diabetes mellitus, genital atrophy was not ascertained. These circumstances cannot, however, be said to speak against the assumption of hemochromatosis. For it is well known and has been testified from several quarters that a marked hemochromatosis may be compatible with the absence of hemosiderin in the skin in spite of dark pigmentation (Björn Knutsen, among others). A liver puncture would have been decisive with regard to an exact diagnosis but owing to the pronounced thrombopenia of the patient this intervention was refrained from.

In view of our present knowledge of the indications for folic acid therapy, it does not appear particularly remarkable that the treatment of a hyperchromic and macrocytary anemia of the refractory type should turn out successful. However, the present case seemed an instructive one and to warrant publication on account of its response to folic acid in a final stadium, indistinguishable from an aplastic anemia. Whenever the latter diagnosis has been made, it has rarely been possible to follow the course

from the onset of the anemia. It is, no doubt, a priori difficult to decide against the diagnosis of an anemia in an aplastic final stadium belonging to one of the groups affected by folic acid. A test may, therefore, often be justified, especially as the therapy does not require long time in order to decide this point. Entirely in agreement with earlier experience on this subject, cases of this kind are probably rare. However, this does not alter our opinion or actions in principle.

Summary.

A man, aged 64, is reported who had, from the start, a refractory anemia of the hyperchromic and macrocytary type with hypercellular bone marrow which, after an observation period of 2½ years, ended up in an aplastic stadium with a marked reduction of the erythropoiesis in the marrow, erythropenia, leucopenia and thrombopenia in the peripheral blood. Towards the end, a conspicuous dark pigmentation of the skin rapidly manifested itself, being all likelihood an indication of hemochromatosis. At this final stage, folic acid was introduced with striking effect. The blood values were normalized to a large extent within a fortnight. However, thrombopenia and a relative lymphocytosis remained. The sternal marrow was normalized to some degree. This case seems to urge to tests with folic acid therapy even in aplastic anemias, since the majority of anemic forms may transform to or end as aplastic anemia and one does not always know the form of anemia occurring at the onset. Folic acid is clearly of no value at primary aplastic anemia.

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On the Effect of Betaine on the Course of Hepatitis Acuta.

By

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(Submitted for publication September 1, 1947.)

It has been known for a long time that betaine, on account of its labile methyl groups, is capable of increasing the formation of choline in the animal organism. It is therefore also capable of preventing the occurrence of fatty liver caused by a choline deficiency. Betaine seems to be an extremely efficient donator of methyl groups, since choline formed from betaine occurs in the tissues almost equally rapidly after the ingestion of betaine as after the ingestion of choline (5). However, it affords a somewhat less rapid and somewhat less efficient protection against fatty liver than does choline (2, 4).

In the course of some investigations on the effect of betaine on the ability of the human organism to transform glycocyamine into creatine by a methylation process (1), some patients suffering from hepatitis acuta were subjected to a prolonged treatment with betaine. A discussion of the effect of this treatment on the course of the disease may have a certain interest, since, as mentioned in a previous paper (1), some reports have been given in the literature on the effect on liver diseases of other compounds which are also capable of preventing the occurrence of fatty liver. A treatment of this kind must be considered valuable in cases of liver cirrhosis on alcoholic basis. However, in cases of acute hepatitis the effect is extremely doubtful (5), but choline seems to stimulate the appetite in hepatitis patients with an inadequate protein uptake in consequence of their bad general state (3).

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All in all 8 patients, all of whom had been admitted to Righospitalets medicinske Afdeling B on a diagnosis of hepatitis acuta, were treated with betaine in the form of betaine hydrochloride. The amount given was 2 g 4 times daily. The ingestion caused in most of the cases a pyrosis, which could easily be eliminated by means of sodium bicarbonate, and at the end of the treatment none of the patients suffered any dyspeptic inconveniences. The course of the disease was checked by general clinical examinations as well as by weekly blood analyses in order to determine total serum fat, free and bound serum cholesterol, serum creatine and creatinine, hemoglobin, serum bilirubin and sedimentation rate. Venous blood samples were drawn in the morning, before the patients had got any food.

In the results thus obtained no trace of an effect of betaine could be detected. In particular the values obtained for total fat, free and bound cholesterol, creatine and creatinine were unaffected by the treatment with betaine, though theoretically these quantities might be supposed to be most strongly influenced by ingestions of betaine.

In 6 of the patients, of age 21 to 64 years, the course of the disease was typical. It lasted for 20 to 96 days, with an average duration of 65 days. The treatment with betaine lasted from 17 to 60 days. None of the patients had an enlarged liver. A 71 years old woman died from the disease. A male patient (age 38 years) acquired chronic hepatitis; during his stay in hospital his liver was somewhat enlarged, and this symptom remained absolutely unaffected by the treatment with betaine. In none of the patients subjective or clinically objective changes in their state, ascribable to the betaine treatment, could be detected.

As controls we have 13 patients, who in the same period of time had been treated in our department for hepatitis acuta without ingestion of betaine. Their age varied from 19 to 62 years. Their illness lasted from 24 to 60 days, with an average duration of 43 days. None of them showed enlarged liver. One patient died from the disease. The clinical course of the disease was considered identical in both groups of patients; the difference between the two groups with respect to the duration of the disease can be explained by the fact that our material comprises only relatively few cases. Moreover we had the impression that the patients who received the betaine treatment were more strongly attacked by the disease than the majority of the patients in the control

group. Except for this the two groups showed no deviations from one another with respect to the clinical and biochemical course of the disease.

It must therefore be concluded that betaine has shown no effect on the course of hepatitis acuta.

Summary.

8 patients suffering from hepatitis acuta were subjected to a prolonged treatment with betaine. A control group of 13 patients was treated without ingestion of betaine. No definite differences between the two groups with respect to the clinical and biochemical course of the disease could be detected.

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Keratoconjunctivitis Sicca and Chronic Polyarthrititis.

By

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(Submitted for publication September 1, 1947.)

In my thesis 1933 I said: »Every elderly arthritic woman who complains of conjunctival symptoms is to be suspected of having keratoconjunctivitis sicca» and in a later work (1940) I added that the experience from an eye-doctor's reception proves that such is really the case even when the patient only came to try new spectacles. In the same paper I pleaded for a systematic investigation of arthritis cases as regards occurrence of KCS. It is satisfactory to know that such an investigation has now been performed by Stenstam in collaboration with Stig Holm. In the present magazine Vol. CXXVII, p. 130, 1947 Stenstam has scrutinized the material from the internal-medical and rheumatological standpoint. From his work it appears that 10.5 per cent of all cases of primary-chronic arthritis suffer from KCS in a more or less pronounced form. In view of what I have just said this result is rather surprising. Knowing how often arthritis occurs in KCS one might have expected to find in an arthritis material a considerably greater number of cases than 10.5 per cent, the more so as even slight cases are included in the summary as far as I can gather.

As regards distribution between the sexes which in my present material is 93 per cent women and 7 per cent men, Stenstam says that KCS occurs as often in men as in women. It was indeed only to be expected that in a given material of arthritis there would be a number of men with KCS. Moreover there are men free from

arthritis who have KCS. As there were 65 p.c. women and 35 p.c. men, we can also express the relation by saying that both arthritis and KCS are twice as common among women as among men. This preponderance of women in Stenstam's material is still more striking since he declares that the advanced forms occurred «in much greater numbers in women than in men».

Attention was earlier (1943) drawn to this circumstance by Gifford and co-workers who in pronounced cases found only one man to eleven women, thus 91 per cent women. In slighter cases he found 4 men to 17 women, thus 75 p.c. women.

Here is evidently to be found one of the reasons for the varying occurrence of men in the material of Stenstam & Holm and of myself. The question arises: when shall we in early and slight cases diagnose KCS? When a symptom complex is to be defined, it is usual in the first place to examine the typical, fully developed cases. Experience must then show in what measure less pronounced cases must come under the disease. When we are concerned with the colorableness of the eye with rose bengale, we must allow for a slight coloring as an expression of the normal detrition which occurs in all superficial epithelium and there is often a slightly increased coloring *c. g.* in simple chronic conjunctivitis etc. The deciding matter for me in these cases has been the subsequent course. Some of the female cases I have seen have gradually developed into typical cases of KCS from a slight and uncertain commencement. The male on the other hand have either got well or have simply disappeared without more ado. They had either got well or else the discomfort was so slight that they saw no reason to continue the treatment. Whether there was incipient KCS among these cases I am unaware, but at any rate I have not ventured to build on them. The difficulty becomes greater when we consider that Schirman's tear-function test, as he himself urges, is a very rough method the details of which have not yet been in any way standardized. Thus there is no sure method of diagnosing at an early stage. Further information as to these early cases in Stenstam's material would have been of great interest. They were of most frequent occurrence among the male patients. Have they remained constant or have they become fully developed cases of KCS?

Stenstam says: »It appears most natural to regard the KCS syndrome as one of the symptoms of the chronic arthritis picture». KCS can, however, as we know, occur without contemporary

arthritis. In my total material (62 cases) this is so in about 40 per cent. Among pronounced cases Gifford likewise found 40 p.c. without arthritis while in the slight cases arthritis was absent in no less than 80 p.c. Moreover, a number of such arthritis-free cases are described in the literature. For the further investigation of KCS the method adopted seems to be the one used by Stenstam & Holm viz. to take a certain group of diseases and then see how often KCS can be demonstrated in the same. Atrophic rhinitis was once taken as the starting-point in the Ear Clinic of Sabbatsberg Hospital, Stockholm. After having shown that there was no connection between KCS and ozaena the work was discontinued. Mogens Faber (1944) started from xerostomy and found KCS in about half of the cases and unconnected with arthritis. While mentioning xerostomy or »symptoms from the mucous membranes of the mouth and pharynx», to use Stenstam's terminology, there were in my total material 55 p.c. having such symptoms. Gifford found in the slight cases of KCS xerostomy in 25 per cent and in pronounced cases 83 p.c. In the material of Stenstam and Holm these symptoms were found in about one fourth of the cases. When Stenstam discusses the dental status he finds that »it is difficult to determine from this small material whether the KCS material exhibits greater damage to the teeth than do other morbid groups».

Manifestly teeth do not fall out because the eyes are dry. What would have been of interest to know would have been to know how often early shedding of the teeth occurs in cases which at the same time are suffering from xerostomy. It is an old observation that teeth suffer early damage in xerostomy.

Another disease group which has been KCS analysed is the Plumer-Vinson syndrome where, however, according to Franceschetti and quite recently Godtfredsen, no etiological connection can be established. Another group which we may hope will soon become the object of KCS analysis is the skin diseases. Some cases are already described — among them sclerodermia. I myself have followed a case since 1930 — a woman who at the first examination was suffering from acrodermatitis atrophicans Herxheimer and a somewhat uncertain KCS. When I last saw her in 1943 she had a fully developed KCS with xerostomy and advanced atrophy of the skin over practically the whole body. She never had any articular symptoms during the whole of this time.

Consequently, as the KCS syndrom not seldom can appear

without articular affections we cannot say right off that it is a subgroup of chronic polyarthritis. It looks as if, due to Stenstam's work and also to broadened experience as set forth in the literature, arthritis has lost something of its earlier dominance in the symptom complex. It seems still most correct to say that both arthritis and the rest of the KCS syndrome are expressions of a chronic general infection, as I sought to demonstrate in the work I published in 1935.

Stenstam says that the view that arthritis and laboratory finds such as enhanced SR lymphocytes, lowered carbohydrate tolerance etc. are specially typical of KCS or caused by the keratoconjunctivitis symptoms is unlikely. For my part I would say that it is preposterous and it has never been advocated by myself. In my 1935 paper I adduced these reactions to prove that in KCS there occurs a general infection and that in the cases where there is arthritis it is a question of primary-chronic infectious arthritis.

What may issue from the general survey of an internal medicine clientele which we hope will be forthcoming by-and-by, we must wait and see.

One circumstance cannot be disregarded and that is the considerable preponderance of the female sex which all writers have found and which also appears in Stenstam's article. This along with other clinical circumstances points to an endocrine component. Hormone and vitamin analyses have, however, hitherto been negative.

In one of my works I urged that the patients concerned often look older than their real age. I have not tried to provide figures as to the frequency of such cases. Stenstam says now that «in a few cases there was a definite suggestion of senility (2 men and 4 women)». This comprises 13 per cent of Stenstam's material.

It is regrettable that age distribution is not clearly set out in Stenstam's paper. In my 1933 paper I had only two cases less than 40 years of age.

In 1940 I showed that the primary thing in the gland disease of the KCS syndrome seems to be parenchyma disintegration and pointed out the great similarity displayed by the microscopic picture with the changes which Lambert and Yudkin found in these glands in the earliest stage of experimental A-avitaminosis. I wish here to take the opportunity of further underlining the fact that this parenchyma disintegration as a primary gland change in KCS can only be demonstrated in the very first stage of the dis-

ease before the lymphocyte-infiltration has begun and before the corresponding mucous membrane has afforded any symptoms. It is these changes which (of course after consultation with pathologists) I have characterized as an adenopathy and which I have called the primary and specific marks of the gland disease, distinguishing it from other diseases of these organs.

Such seats of disintegration have since been demonstrated also by Radnot who interprets them as a senile phenomenon. According to Buehaly they occur in septic states.

In my thesis of 1940 I showed that symptoms of reduced secretion may occur also in other gland diseases where the parenchyma has suffered secondary injury.

We are still ignorant of what is the final cause of the KCS syndrome. To me it seems most likely that we must reckon with two components, one infectious and one endocrine.

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Renal Osteodystrophy.

Report of a Case.

I

Clinical Aspect

By

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(Submitted for publication August 29, 1947.)

Since Mandel performed his famous operation on the parathyroid gland, in 1925, in a case of osteitis fibrosa generalisata, a large number of works on diseases due to hyperfunction of the parathyroid gland have been published. (See, for instance, Albright, Aub and Bauer, 1934, Hellström 1935, Albright 1941, Hellström and Wahlgren 1944, Snapper 1943, Keating and Cook 1945, Keating 1945.) In these cases of so-called primary hyperparathyroidism, the well-known disorders in the calcium and phosphorus metabolism, with increased serum calcium, a low serum phosphorus content, and increased amounts of calcium and phosphorus in the urine, are found. The clinical symptoms vary. In some cases the dominating signs and symptoms are those from the urinary organs, with nephrolithiasis or calcinosis renalis, which have renal insufficiency as the predominating symptom. In other cases the signs and symptoms from the skeleton are the more marked, with osteitis fibrosa generalisata or osteoporosis. For details as to symptomatology the reader is referred to Albright, Aub and Bauer 1934, Keating 1945, and Snapper 1943. In this primary hyperparathyroidism, operation or autopsy reveals one or more parathyroidal adenomas, or in a few cases diffuse enlargement of all the parathyroids.

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Bergstrand (1941) maintains that even in the case of apparently single adenomas, a general, often adenomatous, hyperplasia of the parathyroidal tissue is found. The causative factor underlying the hyperplasia and hyperfunction of the parathyroids is not known. It has been suggested that the cause might be an exaggerated endocrine influence by the hypophysis (Bergstrand 1941, Wilton 1944 and 1947, Perlman 1944, on the basis of the experimental observations of Anselmino, Hoffman, Herold 1935 and 1944, and other investigators) or a spontaneously arising new formation in the parathyroids.

A generalized enlargement of the parathyroids was observed even in earlier years, in a number of different clinical conditions (Erdheim 1907 and 1914, Bergstrand 1920—21, Pappenheim and Wilens 1935, Gutman et al. 1937). This was the case with rickets, osteomalacia, and chronic renal insufficiency. The cause of this parathyroidal enlargement has been discussed from various aspects, and has not yet been satisfactorily cleared up. The view expressed by the majority of authors is that it is a question of some kind of compensating hyperplasia brought about owing to increased parathormone requirements, the latter, in its turn, being due to disturbances in calcium or phosphorus metabolism associated with the different disease conditions.

It has long been known that in children, conditions of chronic renal insufficiency, in congenital hypoplasia of the kidneys or in strictures of the urinary passages of congenital origin, were associated with skeletal disorders such as are seen in rickets or with disturbances in growth. Such terms as renal rickets and renal dwarfism have been used (see Snapper 1943 and Tomenius 1944). Some of the roentgenograms obtained were strongly suggestive of rickets, others resembled the pictures seen in osteitis fibrosa generalisata. Histologic examination yielded findings such as are obtained in osteitis fibrosa generalisata.

That enlargement of the parathyroids may occur in patients with renal insufficiency was first demonstrated by Bergstrand (1920—21) in patients suffering from chronic nephritis. The same fact has later been confirmed by Albright, Baird and Bloomberg 1934, Gilmour and Martin 1937, and by Albright, Drake and Sulkowitsch 1937, Castleman and Mallory 1937, Ginzler and Jaffe 1941, and others. It was in connection with conditions of renal insufficiency associated over a relatively long period with phosphate retention and acidosis that disease of the bones

resembling osteitis fibrosa was established; in these cases parathyroidal enlargement also was observed at autopsy. The conditions were described as renal hyperparathyroidism or secondary hyperparathyroidism. Since then, doubt has been expressed as to whether it is really a question, here, of hyperparathyroidism in the same sense as in primary hyperparathyroidism, and it has been suggested that the condition be called, instead, renal osteodystrophy. (See Snapper.)

Descriptions of disease conditions in which the renal osteodystrophy has advanced to such a stage as to produce clinical symptoms are much more commonly found with regard to children and young adults than to older persons. This is presumably to be put down to the fact, as Snapper has pointed out, that the congenital anomalies of the kidneys and urinary passages leading to renal insufficiency have this effect early in life, and also that growing bones are more likely to manifest skeletal disorders than a skeleton already fully developed. In the publications I have studied, I have only encountered 9 cases of renal osteodystrophy in persons over 20 years of age (Gutman, Swenson and Parsons 1934, Magnus and Scott 1936, Albright, Drake and Sulkowitsch 1937, Nelson 1937, Castleman and Mallory 1937 — the same cases as Albright 1936 and Albright, Drake and Sulkowitsch 1937 — Bergstrand 1941, Herbert, Miller, Richards 1941, Curtis and Felder 1942, Soffer and Cohn 1943, Wigbey and Hunter 1945). The clinical symptoms in these cases of renal osteodystrophy were caused partly by the kidney damage and partly by the diseased state of the bones.

The signs and symptoms from the kidneys vary according to the nature of the kidney damage. Renal insufficiency with increased non protein nitrogen, acidosis, and retention of phosphate with an increased serum phosphorus content are always observed. As regards the blood chemistry, low or normal calcium values are found; in some cases the values are slightly increased. As in the case of primary hyperparathyroidism, the phosphatase content may vary.

The signs and symptoms from the skeleton, in children and growing persons, resemble those of rickets, and are often associated with disturbances of growth (renal dwarfism), or those of osteitis fibrosa, with deformation of bones and spontaneous fractures and a roentgenogram similar to that obtained in osteitis fibrosa generalisata; in other words, widespread changes which sometimes

take the form of a change in the bone structure (a moth-eaten appearance), more or less advanced mottled rarefactions, or an appearance resembling that seen in osteoporosis. In adults, naturally, only the signs and symptoms of osteitis fibrosa occur.

Postmortem examination of patients who have suffered from renal osteodystrophy reveals general enlargement of all the parathyroid glands. All the glands are enlarged but not necessarily to the same extent. American authors (Albright, Castleman and Mallory) maintain that the hypertrophy is caused mainly by proliferation of the chief cells. In the rare form of primary hyperparathyroidism in which diffuse hyperplasia of the parathyroids is also found, the hyperplasia is due to proliferation of so-called »Wasserhelle» cells (Albright, Bloomberg, Castleman, Churchill 1934, Albright, Sulkowitsch and Bloomberg 1938). In the common form of primary hyperparathyroidism, one or several enlarged glands with parathyroidal adenoma are encountered, and besides these glands there are others of normal size. It may be mentioned in this connection that cases have been described in which the patients originally had primary hyperparathyroidism which led to kidney damage and in which the kidney damage would later have produced a renal osteodystrophy (Johnson 1939, and — less convincing — Downs and Scott 1941).

Calcium salts are deposited in the soft tissues in primary hyperparathyroidism. In most cases the calcification takes place in the kidneys but many other parts of the body may also be affected. In an especially large number of cases the tunica media of medium-sized arteries is the seat of these changes. In renal osteodystrophy, the calcified areas in the arteries are a particularly prominent feature, and in a remarkably large number of cases calcifications occur in the skin and subcutis, usually situated peri-articularly, as Albright points out. (Hubbard and Wentworth 1920—21, Smyth and Goldman 1934, Albright 1936 (same cases as Castleman and Mallory 1937, Albright, Drake and Sulkowitsch 1937), Magnus and Scott 1936, Bergstrand 1941, Herbert, Miller and Richards 1941, Curtis and Felder 1942, Soffer and Cohn 1943.) Advanced vascular calcification and metastatic calcifications in the skin, among other things situated around joints, were also present in the case to be described in the present publication.

The differential diagnosis, in a given case, between renal osteodystrophy and primary hyperparathyroidism may come up against considerable, and sometimes even insurmountable, difficulties.

In its advanced phases, primary hyperparathyroidism may also cause renal insufficiency that may be severe and produce an increased serum phosphorus content. The serum calcium picture may sometimes, but by no means always, be the decisive factor. Definitely increased values point to primary hyperparathyroidism, as does also a marked increase in the amount of calcium secreted with the day's urine. A normal or only slightly increased serum calcium content, as well as a slightly increased, normal or low secretion of calcium in the urine do not decide the question in any direction, since renal insufficiency is capable of modifying a previously increased serum calcium concentration as well as a previously increased calcium secretion. It may be mentioned in this connection that not infrequently the serum calcium is slightly increased or within the normal range in established cases of primary hyperparathyroidism also (Gutman, Swenson and Parsons 1934, Keating 1945, Keating and Cook 1945). The case history, and the establishment of prolonged kidney damage may be of assistance for the differential diagnosis but, as Snapper points out, this is by no means always the case. — Not infrequently, renal affection and disease of the bones are detected simultaneously. The clinical picture, with severe calcification of the arteries and soft tissues in the advanced cases, may sometimes point to the fact that renal osteodystrophy is in question. At a postmortem examination the changes discovered in the parathyroids naturally often decide the question in one direction or the other.

A description of disease of the bones and renal insufficiency in a 40 year old woman, which I interpreted as renal osteodystrophy, will now be given here.

A. M. E. H. Record no. 456/1942, 1745/1943, 122/1944, and 1058/1944. A married woman born in 1909, who was thus 33 years old when we first saw her in 1942. Partus 1935, 1938, and 1939. Menstruation regular. Up to one month before being admitted to the hospital she had run her house herself and cared for her family of 5 persons.

Case history: In 1928 she had cystitis and in 1937 cystopyelitis. When discharged in 1937, and again after her confinements in 1938 and October 1939, she had no albuminuria.

Her present illness had begun about a year before she was admitted, and she complained of fatigue and loss of weight — about 4 to 5 kilos —, and pains in her right heel and leg which she described as rheumatic. At the end of January 1942 she began to experience pains in her right groin on walking or when she stood on her right leg. Because of these pains a roentgen examination was carried out, on Feb. 26 1942, at

the Orthopedic Clinic of the Caroline Institute. The following information was obtained: »In plain views of the pelvis a destruction is apparent in the medial portion of the right ramus of the ischium, covering an area the size of a shell almond. The bone tissue is destroyed in this area and appears to be irregular and porous. No reactive sclerosis is apparent in the adjoining areas. The appearance of the area of destruction is suggestive of the destruction due to a tumour and a further thorough examination seems called for. Further, there is a rarefied area the size of a fingertip in the left ala ilii which is also suspected of being due to a tumour.»

Because of this roentgenogram the patient was remitted to the Caroline Hospital for further examination.

When she was examined in 1942 she was found to be in good health. Her skin was very dark, but as it had been so from birth it could not be attributed any diagnostic significance. It was taken for granted that the roentgenographic findings in the bones were due to tumour metastases and a thorough search for a primary tumour was therefore made, but without success. Roentgen examination of the bones of the extremities revealed a rather vaguely defined rarefaction on the head of the right humerus and another such area in the right tibia. No other areas of destruction were apparent in the bones of the extremities. Roentgen examination of the kidneys revealed that these were unusually narrow and that with intravenous urography no clearly demonstrable secretion was obtained. Extensive calcifications in the glands in the lower part of the abdomen were also observed. Albumin was detected in the urine on a couple of occasions, but at other examinations no albumin could be demonstrated. In the sediment from discharged urine large numbers of white blood cells were observed at times, at others only a few were present. The specific gravity was 1.010—1.008. Cultures made from the urine showed no bacterial growth. Blood pressure, 140/80. Serum calcium, 10.2 mg per hundred ml.

During this period in hospital osteitis fibrosa was not suspected (see the serum calcium), and the patient was discharged, suspected of having multiple metastases in the skeleton without any primary tumour having been discovered. She was put on the out-patient lists.

Her condition did not, however, deteriorate during the summer and autumn months of 1942; if anything, she felt better. In March 1943 her fingertips began to grow larger, broader, and rounder than before, and felt tender. During the summer of 1943 she felt worse — she was weary, had attacks of nausea, ate poorly, and had to urinate often, which she put down to her old cystitis. She had aching pains in various parts of her body, especially in her legs and the right groin. Because of these she limped. Her menstruation was now a little irregular. At the out-patient controls her general condition was not considered to be particularly affected, and she was submitted to another fairly thorough examination. At a second roentgen examination of the pelvis on Aug. 10, 1943, it was found that the bony tissue in the greater part of the pelvis was partly obliterated and somewhat irregular in appearance. Considerable destruction and fracturing was evidenced in both the

superior and the inferior ramus of the right pubis. The bony tissue was also obliterated in the upper portion of the femoral shaft and neck. In the thoracic, lumbar, and sacral segments of the vertebral column the bony tissue was almost totally destroyed, and the vertebrae had a worm-eaten appearance. In addition, widespread areas of calcification had developed in the blood vessels of the pelvis minor since the roentgen examination in February 1943.

Because of these extremely extensive changes in the skeleton as compared with the patient's relatively unaffected state of health it seemed from the clinical aspect as though a systemic disease rather than diffuse metastases must be in question. Roentgen examination of the other parts of the skeleton revealed osteoporosis and extensive obliteration of the bony tissue. The tissue appeared, to be threadbare and spotty. In the terminal phalanges of all the toes and fingers the bone tissue had in places completely disappeared and the bone had evidently been replaced to some extent by some kind of osteoid tissue. In the middle of the left femur there was a cystic rarefaction but there were otherwise no cysts. The skull showed slight thickening of the calotte. The bone markings had an irregular, spongy appearance, which was due in part to increased sclerosis and in part to small, fine rarefied areas. The roentgen diagnosis now made was Recklinghausen's disease. The kidneys were also seen, now, in the roentgenogram, to be fairly small, but no concretions or calcified foci were visible. As regards the blood chemistry, the serum calcium was now 10.1 mg per hundred ml, the serum phosphorus 10.0 mg and the non protein nitrogen 134 mg. In other words, renal insufficiency.

The patient was admitted again to the clinic in September 1943. She was in a fairly good state of health. She had an anemia of about 8.5 g hemoglobin per 100 ml blood and 3.2 million reds. Her terminal phalanges were short and broad, and almost ball-like. Her nails were only one-third of the normal length. Such changes in the terminal phalanges of the fingers are not infrequently mentioned in osteitis fibrosa generalisata. The features of particular interest in this case are the renal insufficiency and the blood chemistry. During the whole of this period in the hospital the urine displayed isosthenuria with a specific gravity of 1.010. Heller's test was weakly positive, and there were a few white cells and no red cells or cylinders in the sediment from drawn samples. Cultures showed no bacterial growth. The diuresis lay between 1,500 and 2,000 ml per day. The non protein nitrogen was 150 mg per hundred ml on her admission, but one week later it rose to 230 mg in connection with a threatening uremic state accompanied by nausea and vomiting. In conjunction with this there was tachycardia and a poor pulse. This crisis, as well as the patient's dark colouring, caused us to suspect an Addison crisis and we therefore administered Doea and cortin. Under this treatment, together with fluids administered parenterally (intravenous drip) the patient improved, the uremic state being checked and the non protein nitrogen dropping to 118 mg per hundred ml. An inulin test showed a filtration of 8 and 9 ml per minute; thus, an extremely poor renal function.

Table 1.

Date	Serum Ca mg per 100 ml	Serum phosphorus mg per 100 ml	Blood chloride mmole per L.	Albumin %	K mg per 100 ml	Na mg per 100 ml	N. P. N. mg per 100 ml	Urine Ca g/day's urine
31. 8	10.1	10.0						
13. 9				9.7			150	
15. 9	9.6	10.7		9.7		317		
17. 9								0.08
21. 9							230	
23. 9							230	
24. 9		10.6	85	6.9			200	
26. 9							137	
2.10							118	
15.10			73	8.6	25.8	309	100	
19.10	10.3	7.3						
26.10								0.13
28.10	10.2	10.0	90	8.2	24.4	296	114	
16.11								0.122

The blood chemistry is shown in table 1.

Hamilton's test, performed on Sept. 19, showed that there was no increase of parathormone in the blood. The alkali reserve on Sept. 24 was 18.5 mmole per liter (= 44 vol. per cent of CO_2). Her blood pressure was normal now as it had been during the previous hospital stay — 135/90. During this period in hospital a calcareous shield about 2.5×2.5 cm in size appeared in the skin of the abdomen.

She was discharged about the middle of November (18/11) 1943 and was then a little better. She had no pains and no nausea. The old pains in legs and hips, especially in the right hip on walking, returned after a couple of weeks. The nycturia was the same as before. Her weariness was increasing.

She was admitted again on Jan. 18, 1944. Her condition was then about the same as when she was discharged. The urine findings and the diuresis were the same, and the blood pressure was normal as before. The blood chemistry is shown in table 2.

She was discharged on March 4, and for a time she was fairly well, but she soon became worse again and her old pains returned. Her weariness increased to such an extent that she had to lie in bed most of the day. When walking she had a strong feeling of weakness and a rapid heart beat. She had nycturia but no swelling of the legs.

She was re-admitted on June 7, 1944. She was now worse. Her muscles were poorly developed and tender to palpation. Tenderness was also experienced on palpation over superficial bony parts, with the exception of those of the head. Over the left elbow region a tender firm mass had developed, which was proved by roentgenography to be due to calcification in the musculature and the subcutis. Calcified areas had also formed again in the skin over the abdomen. These areas increased

Table 2.

Date	Serum Ca mg per 100 ml	Serum phosphorus mg per 100 ml	Blood chloride mmole per L.	Albumin %	K mg per 100 ml	Na mg per 100 ml	N.P.N. mg per 100 ml	Urea N mg per 100 ml	Urine Ca g/day's urine
19.1							166		
20.1							161	137	
22.1	11	7.2	66	9.3	20.2	305			
29.1							128		0.099
30.1			75				86	54	
14.2							120	72	0.05
23.2									0.14
24.2									

considerably in extent during the subsequent course and were soon found in patches all over the abdomen and in the skin over both breasts. A roentgenogram of the skeleton revealed changes approximately the same as in 1943. The calcifications in the arterics of the arms were now demonstrable by roentgenography. The kidneys were the same as before, small and without noticeable calcified foci. The urine picture and the diuresis were still about the same. Blood pressure normal. For the blood chemistry, see table 3.

In the beginning of July the amount of urine decreased and on July 11 the patient died.

Postmortem examination revealed five enlarged parathyroid glands having a total weight of 3.2 g. The autopsy findings are to be described by Dr. Enell (Enell 1948).

Summing up, it may be said that we have here a case of osteitis fibrosa generalisata with a strong tendency to calcification of the soft tissues. The blood calcium was normal, the secretion of calcium in the urine was not increased, and a marked renal insuffi-

Table 3.

Date	Serum Ca mg per 100 ml	Serum P mg per 100 ml	Blood chlorido mmole per L.	K mg per 100 ml	Na mg per 100 ml	N. P. N. mg per 100 ml	Urea N. mg per 100 ml
7.6	10.7		82			210	
9.6				21		257	157
13.6		12.2			282		
17.6						300	
27.6	10.2					280	
30.6						368	
3.7						240	

ciency, with increased non protein nitrogen and increased blood phosphorus, was present the whole time she was under observation.

It is of some interest to endeavour to clear up the nature of this renal insufficiency. The findings from the urine indicated contracted kidneys, and this assumption was also confirmed at the postmortem examination. As the blood pressure was normal the whole time it is unlikely that the patient was suffering from chronic nephritis or the final stages of a malignant hypertension. A normal blood pressure in association with a contracted kidney leads the thoughts most naturally to chronic pyelonephritis. We do not know for certain whether the patient had this disease or not, but we do know that she had cystitis in 1928 and pyelocystitis in 1937, and that she did not have albuminuria in October 1939. These data neither disprove nor prove the possibility of a state of renal insufficiency over a period of years. They indicate that such a state may have been present, inasmuch as urinary passage infections are mentioned in the history.

Clinical observations likely to indicate primary hyperparathyroidism were never obtained, as the serum calcium and the secretion of calcium in the urine registered normal values at all examinations, or was not increased above 200 mg of Ca per day. On the basis of the clinical data alone, however, it is not possible to state with complete certainty that this was not a case of primary hyperparathyroidism that came under observation only after an advanced renal insufficiency had developed. The renal condition may have caused phosphate retention and a depression of the serum calcium values, and prevented the secretion of increased amounts of calcium with the urine. Such an occurrence is known in cases of primary hyperparathyroidism.

As regards its clinical type, the case tallies remarkably well with the previously mentioned cases of renal osteodystrophy, with advanced arterial calcification and peri-articular calcifications in the soft tissues. This fact, as well as the absence of features suggestive of primary hyperparathyroidism, and the presence of diffuse parathyroidal enlargement proved at autopsy, all seem to me to indicate that this was a case of renal osteodystrophy.

Summary.

A case of renal osteodystrophy in an adult is reported. The signs and symptoms were those of osteitis fibrosa generalisata. There was a strong tendency to calcification of the soft tissues. The serum

calcium was normal, the secretion of calcium in the urine was not increased. There was a marked renal insufficiency with increased non protein nitrogen and increased serum phosphorus. Clinically this case tallies very well with previously published cases of renal osteodystrophy in adults. The autopsy findings (Enell, *This Journal* 1948) support the diagnosis of renal osteodystrophy.

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Renal Osteodystrophy.

II.

Pathological-Anatomical Account.

By

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(Submitted for publication August 29, 1947.)

In connection with the above-described case of *ostitis fibrosa generalisata* (Oldfelt 1948), which gives great differential diagnostic interest, I will give a brief account of the macro-pathological and micro-pathological findings.

At the autopsy were found five glandular formations, three of which lay on the dorso-lateral edge of the left lobe of the thyroidea (Fig. 1). Thus there was an aberrant parathyroidea gland. The glands varied in size from that of a grain of rice to that of a hazelnut, and their total weight was 3.2 g, as against the normal 15 cg. The enlargement of the different glands was diffuse without nodulation; they were firm and delimited from the surrounding tissue by a thin capsule of connective tissue. Histologically they all exhibited a fairly homogeneous picture with a great abundance of cells, and here and there they were interspersed with coarse connective tissue septa. In places there were clearly alveolar structures with small aggregations of cells, separated by thinner septa, in which ran capillary vessels. In other places the cells were close together, without alveolar structure. The tumour had a remarkably low fat content and also but little colloid. The cells were polygonal with mediumly large round and relatively chromatinrich nuclei. The cytoplasm was light and as clear as water. The fairly homogeneous structure and the absence of pronounced adenoma for-

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nation conforms most closely with a diffuse parathyroideal hyperplasia of the secondary type.

In addition it may be mentioned that other endocrinous organs, such as the thyroidea, suprarenal glands and pancreas, exhibited



Fig. 1.

normal microscopic and macroscopic pictures. It is regrettable that no post-mortem examination was made of the skull, so that any possible changes in the hypophysis could have been revealed, for, according to Wilton's theory 1944, Engel-Recklinghausen's disease with hyperparathyrosis is caused by an excess production

of parathyrotropic hypophysis anterior lobe hormone. However, no clinical or pathological-anatomical signs indicating disturbances of the other functions of the hypophysis could be established in this case.

As renal disturbances have proved sometimes to yield pictures resembling *ostitis fibrosa*, such as Bergstrand has reported, special interest was devoted to the kidneys. They were very small and



Fig. 2.

shrivelled, weighed $\frac{1}{3}$ of the normal weight, altogether 100 g. Macroscopically they exhibited the pictures of severe nephrosclerosis with granulated surfaces and greatly reduced cortical layers (Fig. 2). Even macroscopically a number of small cysts were seen in the parenchyma. There were no stones in the renal pelvis. The microscopic picture was very varied with great arteriolosclerosis, while the somewhat larger vessels were relatively thin-walled and but slightly sclerotic. On the other hand, in the coarser renal vessels of the size of art. arciformes there were extensive intima calcifications of the Jores' type. Here and there in the parenchyma there were strongly necrotic parts, and abundant calcium and fibrosis with round cell infiltration in the interstitial connective tissue.

Abundant pathological calcifications were also met with in the other organs of the body. In the clinical report mention has already been made of the skin infiltrations and the subcutaneous precipitations. Microscopically the skin calcium lay in the corium on the border to the subcutis surrounded by a zone of granuloma tissue and foreign body giant cells.

In the heart there was severe sclerosis of the endocardium, which, *inter alia*, at the base of the right aortic valve, was of the shape of a thin shield of the size of a farthing. In the myocardium were found fairly large, partly confluent, fibrous and relatively loose foci with calcifications. Here and there were also seen clear deposits of calcium in the muscle fasciculi bundles, the structure of the muscle fibres being retained in places. Around the calcium there was an acute inflammatory reaction. Further, there was a fibrinous pericarditis.

Of the large and moderately large vessels it was above all the femoral, uterine and hemorrhoidal vessels which were affected, but even the vessels of the spleen were clearly calcified. The mesentery exhibited calcifications at the coecal pole.

Apart from the heart, the lungs are also in the first place the seat of pathological calcareous changes in cases of *ostitis fibrosa*, which appeared in this case, too. The calcinosis had invaded the bronchial cartilage of the lungs but was also met with in the pleurae in the form of thin sheets of calcium. The lungs were filled with fluid and had a strongly uremic smell. The immediate cause of death was considered to be uremia.

No deformities were found in the vertebrae. The spongy tissue in the skeleton was denser than usual, pale, of osteoid type, and very easily cut into. The corticalis in the long hollow bones was also brittle and could be whittled away. In these latter bones there was an abundance of gelatinous pale brownish-red bone marrow. Microscopically pronounced osteoclastic bone destruction and bony trabeculae with signs of decalcification were seen, but on the other hand, no signs of the formation of new bone. Thus it was a matter of diffuse disintegration of bone, as is occasionally seen in similar cases.

On the whole the other organs exhibited normal pictures. The primary factor of the hyperplasia of the parathyroidea cannot be determined in this case with the guidance of the macroscopical and microscopical observations.

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Book Review.

Eduardo Coelho: La pathogénie des altérations électrocardiographiques de la péricardite. 74 pages, 58 illustrations. Lisboa 1947.

The author's intention has been to solve the problem of the pathological background to the RS—T displacements and T wave inversions in acute pericarditis. He presents in detail quite a few cases of different kinds of pericarditis and discusses the electrocardiograms and in some cases also the findings at necropsy. His theory is that the electrocardiographic changes are due to an irritation of the epicardium, which, in turn, causes an injury current. However, the argument against so-called *subepicardial* damage (*i. e.* damage to the layers of the myocardium immediately beneath the epicardium) is rather weak, as it is based only upon 6 necropsy studies, details of which are not given in any case. There is no attempt to explain how the injury current in the epicardium may influence the myocardium. The book gives a good clinical and electrocardiographical survey of the acute pericarditis, but cannot be said to have solved the problem about the ultimate origin of the electrocardiographic changes in that condition.

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Book Review.

The Medical Annual, a year book of treatment and practitioner's index. Sixty-fifth year, 1947. Editors: Sir Henry Tidy, K. B. E., M. A., M. D. (Oxon), F. R. C. P., and A. Rendle Short, M. D., B. S., B. S. C., F. R. C. S.

Bristol: John Wright & Sons Ltd., London: Simpkin Marshall (1941) Ltd. Baltimore: The Williams & Wilkins Company. Toronto: The Macmillan Co. of Canada Ltd. Melbourne: W. Ramsay. Sydney: Angus & Robertson Ltd.

The 65th volume of this most useful year book has now appeared. It affords an excellent review of the year's work by a great many of the most prominent British medical authors. Among the specially topical and more comprehensive articles I would mention: Tracer substances and their uses, Rubella and congenital malformations, Streptomycin, The surgical treatment of hypertension, Thiouracil in the treatment of thyrotoxicosis, The congenital coarctation of the aorta and the original contribution of Crafoord to its surgical treatment etc. For the first time the Medical Annual contains an article on social medicine.

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Hemorrhagical Thrombocythemia.

By

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(Submitted for publication September 9, 1947.)

It is well known that in cases with a reduced number of thrombocytes a hemorrhagical diathesis is often found though the relation between the degree of thrombopenia and the tendency to hemorrhage is by no means constant. In other cases of hemorrhagical diathesis it has not been possible to demonstrate thrombopenia and sometimes the number of platelets has even been increased. In such cases the possibility of qualitative changes in the platelets as a cause of the hemorrhagical diathesis has been considered.

An increase in the number of thrombocytes has been observed with a number of different conditions mentioned in the already existing publications as: Physical strain, traumatic lesions, confinements, hemorrhage. An increased number of thrombocytes has also been found in patients recovering from infectious diseases, with chronic infections (tuberculosis, septicemia), malignant tumours, after operations, especially splenectomy, following blood transfusions, liver therapy, and at remissions in pernicious anemia. In most of the cases mentioned the increase of thrombocytes was transitory and seldom very large, the number rarely exceeding 1 million per mm^3 . A more permanent increase has been observed in cases of true polycythemia, myeloid leucemia, malignant lymphogranulomatosis, and following splenectomy. With the last named condition as many as 2 millions per mm^3 have been observed.

In these cases of an increased number of thrombocytes there was as a rule no increased tendency to hemorrhage, although it might

occasionally be observed. With regard to true polycythemia this fact is well known. Following splenectomy, Nathan and Rosenthal (8) in some cases observed a very large increase of thrombocytes to 1 million or more sometimes with repeated thromboses and consequent hemorrhages. Minot and Buckman (7) state that with chronic myeloid leucemia hemorrhagical diathesis may be observed as ecchymoses, epistaxis, and hemorrhages following tooth extractions also with a normal or increased number of platelets (up to 1.5 millions). Since 1920 reports have been published on a number of unusual cases which, under different names such as hemorrhagical thrombocytosis or primary thrombocythemia, presented the combination of a high number of thrombocytes and hemorrhagical diathesis. All the cases described are illustrative of the function of the platelets. In the present paper a report on a case observed is given together with a survey of the facies morbi and some remarks concerning the supposed nature of the disease.

Case Record: H. T. N. Male. Born 1903. No similar illness in family. No major illness previously.

Admitted Aug. 28th, 1942. *Discharged* Oct. 10th, 1942. (Case Book 2150/1943.) *Diagnosis:* Hematomyelia. A few weeks before being admitted to hospital the patient began to suffer from paralysis and paresthesia of the legs. Examination showed:

Hemoglobin 130 %. SR: 1 mm/1 hour. Blood pressure 120/60 mm. Spinal fluid: cells 4/3, albumen $> 1/10 < 1/15$, globulin 0. Wassermann reaction \div . Physical examination: nothing abnormal, in particular no enlargement of liver or spleen.

Readmitted Nov. 3rd, 1943. *Discharged* Dec. 11th, 1943. (Case Book 2150/1943.) *Diagnosis:* Gastroduodenitis

Hematemesis, melaena
Thrombocythemia.

Physical examination: nothing abnormal, in particular no enlargement of liver or spleen.

Ewald test meal: 28 + 26 cc. Kongo 65, Phenolphthalein 70.

Feces: $\div \rightarrow 0$ blood with benzidine. Proctoscopy: nothing abnormal. X-ray: slight indication of gastroduodenitis, but no demonstrable ulcer, elongation of the colon.

Blood-urea: 0.074 %. Ascorbic acid in serum: 0.08 %.

Blood: Hemoglobin	89	—————→	98
SR	7		7
Erythrocytes	3.64 mill.		5.3
Index	1.22		0.93
Leucocytes	31,000		19,500
Thrombocytes	932,000		625,000

Icteric index	4	4
Bleeding time	2 minutes	
Coagulation time	1.5 minutes	
Prothrombin time	normal	
Erythrocytes: Anisocytosis	(+)	+
Megalocytosis	(+)	0
Leucocytes: Neutrophile segmented nuclei	73%	71%
Neutrophile staff nuclei	2%	1%
Monocytes	4%	8%
Eosinophile	5%	8%
Lymphocytes	16%	12%

Sternal bone marrow: Differential count gave per 100 leucocytes:

Promyelocytes	1
Myelocytes, neutrophile	4
Metamyelocytes	17
Leucocytes, neutrophile staff nuclei	24
Leucocytes, neutrophile, segmented nuclei	40
Erythroblasts, basophile	4
Erythroblasts, polychromatic	9
Erythroblasts, hemoglobinuous	20
Megacaryocytes	1
Hematocytoblasts	1
Monocytes	3
Plasma cells	1
Lymphocytes	11

(Conclusion: Hyperplastic bone marrow with a shift to the right in granulopoiesis and very slightly increased erythropoiesis.)

In 1945 the patient again has hematemesis (more than one litre).

In 1946 jaundice for ten days.

In 1947 the patient was examined at the Out Patients' Department and stated that he felt tired (see below).

Admitted for the 3rd time Feb. 18th, 1947. Discharged Feb. 28th, 1947. (Case Book 307/1947.) Diagnosis: Hemorrhagic Thrombocythemia. The patient complained of tiredness, occasional nose bleeding and sudden extinction of the lower part of the visual field of the right eye six months before.

At the physical examination the spleen was observed 1 cm. below the curvature (the enlargement was verified by X-ray). No enlargement of the liver. Other organs normal. The patient's appearance was unlike that of one suffering from polycythemia.

Laboratory findings:

Blood:	Jan. 15th	Feb. 20th
Hemoglobin	59	95
SR	5	1
Erythrocytes	4.90 mill.	5.9

Index	0.61	0.86
Leucocytes	19,000	19,000
Thrombocytes	850,000	900,000
Icteric index	4	4
Bleeding time	1 minute	0.5 minute
Coagulation time	1.5 minute	1.5 minute
Capillary resistance (Göthlin)	no petecchiae	no petecchiae
Fragility: beginning hemolysis ...		0.40 % NaCl
total hemolysis		0.24 % NaCl
Erythrocytes:		
Anisocytosis	++	+
Poikilocytosis	+	0
Polychromasia	0	0
Megalocytosis	0	0
Normoblasts	0	0
Jolly bodies	not examined	++
Leucocytes:		
Neutrophile, segmented nuclei....	75 %	84 %
Neutrophile, staff nuclei	2 »	0 »
Eosinophile	4 »	6 »
Monocytes	2 »	1 »
Lymphocytes	16 »	8 »
Plasma cells	0 »	1 »
Myelocytes	1 »	0 »
Thrombocytes: greatly varying in size, many large cells.		
Sternal bone marrow: Differential count gave per 100 leucocytes:		
Promyelocytes		7.5
Myelocytes, neutrophile		25.0
» , eosinophile		2.5
Metamyelocytes		10.0
Leucocytes, neutrophile, staff nuclei		9.0
» , » , segm. »		29.5
» , eosinophile		3.5
Erythroblasts, basophile		2.5
» , polychromatic		5.0
» , hemoglobinous		6.0
Megacaryocytes		1.0
Hematocytoblasts		3.5
Reticulum cells		1.0
Monocytes		2.5
Plasma cells		1.0
Lymphocytes		3.5

There were plenty of megacaryocytes, some of them displayed typical Wright figures, but on the whole the megacaryocytes were of a rather mature type with greatly segmented nuclei. The less mature types appeared in smaller numbers. Some thrombocytes were found which

were not definitely abnormal; they were mostly present in groups and as a rule in connection with the megacaryocytes.

(Conclusion: Hyperplastic bone marrow with a shift to the left and a slightly increased number of megacaryocytes.)

Urine: No sugar, blood, or pus, but albumen (trace —1 ‰).

Microscopical examination: Once no pathological formed elements, a second time one or two erythrocytes.

Urea clearance: standard 1) 68 % of normal; 2) 65 % of normal.

Blood pressure: 160/150—165/100—155/85. Blood urea 0.043 %. Wassermann and Kahn reactions: negative. Mantoux test +. Feces: 0 blood with benzidine. Takata test: negative. Electrocardiogram: Rhythm regular, P-wave inverted in CF_2 and IVF, QRS_3 bifurcated, T_3 isoelectric. Lack of positive initial deflection in CF_2 .

Determination of field of vision: narrowing of the visual field in the two lower quadrants of both eyes (abolishment of ab. 30°). The disc of the right eye was slightly paler on the temporal side than on the left side. The right superior temporal artery was very narrow exhibiting a pronounced spasm at its branching off, and the blood supply was very poor in the peripheral part. No hemorrhage or exudations. No venous stasis. X-ray examination: Heart and lungs normal. Some enlargement of the spleen.

Descriptions of ten similar cases have previously been published by di Guglielmo (5), Epstein & Kretz (3), more detailed by Epstein & Goedel (2), Drake (1), Uotila (12), Rowlands & Vaizey (two cases, 10), Reid (9), Forsell (4), Söderström (11), and Lebel (6). On basis of the 11 cases the facies morbi may be summarised as follows:

The disease occurs chiefly in elderly patients. The patients described were 40—71 years old. Seven of them were men, three women, in one case the sex of the patient was not stated. A tendency to hemorrhage and venous thrombosis is characteristic of the complaint, also a considerable increase in the number of platelets, often polycythemia, a moderate increase in leucocytes, particularly neutrophile, eosinophile, and basophile, as well as monocytes, and lymphopenia. In the bone marrow hyperplasia with an increased number of megacaryocytes was observed. Bleeding time may be prolonged. Coagulation time, prothrombin index, and sedimentation rate of erythrocytes were normal. The spleen and sometimes the liver, too, were often enlarged.

The nature of the cases described is a matter of controversy. Drake (1) includes them under myeloid leucemia, but there seems to be no basis for this theory. Epstein & Kretz (3) and Epstein & Goedel (2) are inclined to consider it a disease sui generis, the

affection of the spleen being primary. Uotila (12) and Forsell (4) support this view, whereas Söderström (11) and Lebel (6) maintain that the disease should be classed among the polycythemias where similar signs and symptoms have been observed. It may be indisputable that most of the symptoms demonstrated may be present in true polycythemia, but the cases present so many characteristic features that it seems worth considering the possibility of a special disease. In this connection the following facts should be borne in mind:

The erythrocyte count: In the majority of cases a definitely pathological increase was found, in others not. Drake found a maximum value of 5.8 mill., Reid (9) 5.65 mill., Söderström (11) 5.6 mill., and the writer 5.9 mill. When considering the figures the hemorrhage presented by the patient must be taken into account as it may conceal polycythemia. In the first case described by Rowlands & Vaizey (10) 2.8—4.67 mill. erythrocytes were counted during a number of years. The patient in question undoubtedly suffered from sprue, and it is doubtful whether the case can be classified with the illnesses described in the present work as the hemorrhagic diathesis was not very evident.

Morphology of the erythrocytes: In true polycythemia very few or no nucleated types are usually found. In some cases of hemorrhagic thromboeythemia a considerable number of nucleated types were observed. In about half of the cases of hemorrhagic thromboeythemia a considerable number of Jolly bodies were found. This phenomenon is not characteristic of polycythemia, but often observed following splenectomy.

Thrombocytes: In polycythemia some increase is generally observed but not so extremely large as in hemorrhagic thromboeythemia. In six of the eleven cases described more than two millions were found, in one case as many as five millions. Moreover, in some cases of hemorrhagic thromboeythemia pathological thrombocytes were found — irregular, of very varying size, in some instances giant cells.

Bleeding time: In polycythemia this is not prolonged, whereas in five of the eleven cases of hemorrhagic thromboeythemia a prolongation was observed which, however, did not prove constant when the tests were repeated. Accordingly, the hemorrhagic diathesis was more pronounced than in true polycythemia.

Spleen: In six cases the spleen was constantly enlarged, in one temporarily enlarged in connection with a febrile infection. These

symptoms are quite consistent with polycythemia, but necropsy revealed quite different conditions.

Necropsy examination: Results of post mortem examination only available in two cases. (No particulars of the case described by Guglielmo (5) were available.) Epstein & Goedel (2) found extensive arteriosclerosis in the spleen and considerable atrophy of the actual splenic tissue, conditions quite different to those revealed by necropsy in true polycythemia. In spite of existing similarities the authors reject the diagnosis of polycythemia on account of the results of the necropsy examination. In Forsell's case (4) the spleen was quite small and completely calcified.

Appearance: The appearance of patients suffering from polycythemia is, as well known, characteristic with a deep red, sometimes bluish, colour of skin and membranes. It is surprising that only one instance of this typical appearance is mentioned in the detailed information available about the cases described (Epstein 2, 3). Other patients may have been of the same typical appearance but they are not likely to have been the majority. Lebel (6) expressly states that his patient was not cyanotic or congested in his face, nor was the patient described by the author.

It will be seen that on account of a number of clinical conditions the cases of hemorrhagic thrombocytosis differ somewhat from ordinary cases of polycythemia. We should therefore be justified in regarding them as a special clinical entity. As for the nature of the affection it should be noted that in the only two cases where a post mortem examination was made, the pathological condition of the spleen was found to be quite different from that usually met with in polycythemia. Both cases presented extensive destruction of the actual splenic tissue, in one case due to pronounced atrophy, in the other to atrophy and complete calcification. Under the circumstances we may reasonably suppose that the patients described suffered from a primary affection of the spleen, a theory which has previously been advanced by other workers.

Summary.

1. The author presents a case of hemorrhagic thrombocytosis.
2. Besides is given a review of the cases formerly mentioned in the literature.

3. The nature of the disease is discussed, and the author sustains the theory of a disease *sui generis*, a primary disease of the spleen.

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Technical Errors in the Taking of Electrocardiograms and Consequent Misinterpretation.¹

By

TORJUS MOE.

(Submitted for publication August 28, 1947.)

Sooner or later there may occur in a hospital or in private practice the following errors during the taking of electrocardiograms:

- 1) The so-called coupling errors: The electrodes for the different leads are interchanged.
- 2) Breach of lead, due either to failure to make contact at one of leading-off places or to interruption of one of the leads.

Other technical faults, such as badly charged battery, will easily be discovered by measuring the voltage, which must be always done. Likewise, restlessness in the patient (tremor, voluntary contraction of muscles etc.), external disturbances of alternating current and error in time-taking will only lead to "bad" electrocardiograms, but not to misinterpretations.

When the first-mentioned errors lead to more or less abnormal electrocardiograms, the mistake will easily be recognized. But when we get an electrocardiogram greatly resembling well-known pathological forms, it may be regarded as having been properly taken and will consequently be wrongly judged, so that heart disease will be diagnosed. As such electrocardiograms are known to occur in practice and are then incorrectly judged, it is justifiable to draw attention to electrocardiograms of this kind, which may be wrongly interpreted even by experienced doctors. The reason

¹ Demonstrated at meeting of the Internal Medicine Society, 1/15 1945.

is that the doctor never once thinks of the possibility of technical errors and overlooks small details which would have betrayed them.

1. Coupling errors: Interchange of electrodes has previously been mentioned by Olof Nordenfeldt (3), who among 8,800 electrocardiograms taken in the course of four years (N. B. It was the same nurse who had taken the electrocardiograms during all that period) found 19, or 2.2 per mille, where the situs inversus electrocardiogram was due to misplacement of the arm electrodes, while only 2 were due to inversion of the heart.

White (5) and Korth (2) remarks that, before diagnosing the typus inversus electrocardiographically, one must always make sure that the arm electrodes have not been misplaced. Warburg (4) states that the frequency of genuine typus inversus (dextrocardia) is about 1 per mille in all children of school age. Abbott (1) reports that out of 1,000 patients with congenital heart disease 18 had "isolated" dextrocardia and 11 dextrocardia with situs inversus also of other organs.

Interchange of the arm electrodes is the most frequent of the 5 possible misplacements that may occur. The reason for this probably is the following: Red and yellow are, as we know, the colours for the arm electrodes, but the mistake arises because the nurse stands with her right arm turned toward the patient's left, or vice versa. She associates the colours with her own right and left arm respectively. Even nurses with long experience may make this mistake.

Some time ago, a patient brought to the author a situs inversus electrocardiogram (negative P-QRS and T in Lead I), where the arm electrodes had been interchanged. The doctor, who had only received the electrocardiogram from the nurse and had not seen the patient, interpreted it as indicating: Right preponderance, myopathia, coronary disease? On control examination the patient was found to have an entirely normal electrocardiogram, normal findings over the heart and normal blood pressure. She had stabbing and pressure pains in the cardiac region, otherwise no subjective symptoms, and she had thus been living for a year in the belief that she had heart disease.

There shall here briefly be discussed the five possible kinds of electrocardiogram that may arise from error in coupling. (Fig. 1.) The electrocardiograms were taken from a person with a sound and normally situated heart.

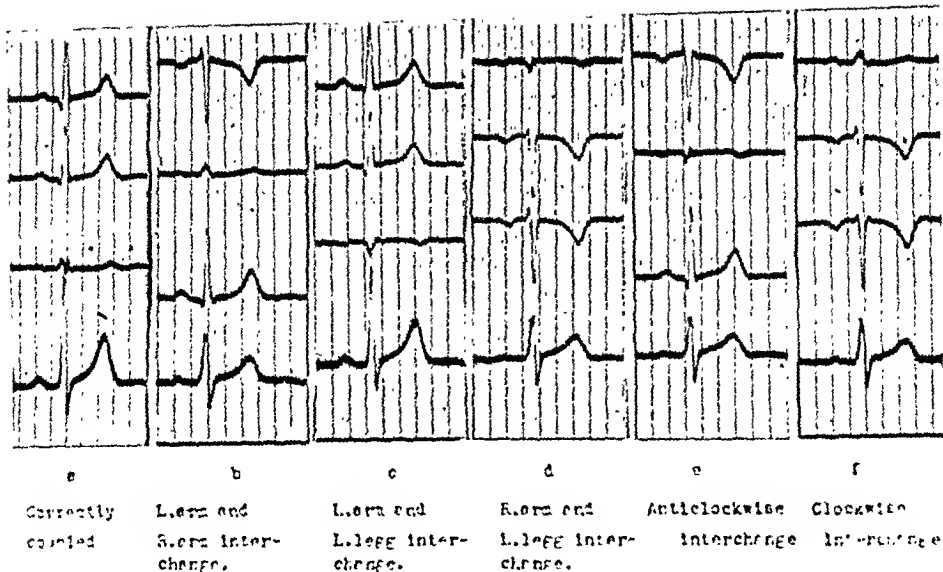


Fig. 1.

Fig. 1 a. Shows the electrocardiogram taken with correct coupling.

Fig. 1 b. Shows an electrocardiogram in which the right and left arms were interchanged. We see that it entirely resembles a dextrocardia electrocardiogram: negative P-QRS and T in Lead I.

Fig. 1 c. Shows an electrocardiogram in which the electrodes for the left arm and the left leg have been interchanged. It resembles an electrocardiogram with left axis deviation: negative P-QRS and T in Lead III, that is to say, the direct opposite of the dextrocardia type seen in Fig. 1 b. Such an electrocardiogram may be seen in persons with sound heart with highly-placed diaphragm and simple transverse position of the heart (in persons of pyknic build, in pregnancy, meteorism). This mistake in coupling will therefore not have any consequences in case of normal hearts.

Fig. 1 d. Shows an electrocardiogram in which the electrodes for the right arm and the left leg have been interchanged. Here we have an entirely abnormal electrocardiogram with negative P-QRS and T in all three leads from the extremities. In Einthoven's triangle the electric axis would have to be directed in a manner entirely opposite to the normal in order to obtain such an electrocardiogram. In other words: the heart would have to lie with the apex upwards to the right and the base downwards to the left, which cannot occur. If we turn the electrocardiogram upside down and look at it in a mirror, we get the correct electrocardiogram. The completely abnormal appearance (merely the fact that we have here a negative P-QRS and T in Lead I, which, as stated, can be seen only in case of dextrocardia) will at once lead us to think of wrong coupling.

Fig. 1 e. Shows interchange of all electrodes in anti-clockwise direction. This electrocardiogram is suggestive of an old infarction in the anterior wall. We note, however a small positive R in Lead I (that is to say, no deep Q), as well as negative P-QRS and T in Lead I, which, as stated, can be found only in case of dextrocardia. Likewise the entirely normal Lead IV would suggest the necessity of control examination.

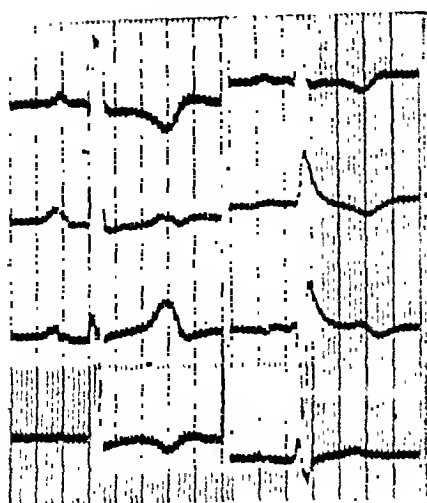
Lead IV (the chest lead) will not show any alteration of importance even if the leads from the extremities (the indifferent electrodes) are interchanged. The chest conduction wire runs quite separate from the wires leading to the extremities, so that it cannot be mistaken for one of them. The normal fourth lead will, as stated, be of help in detecting abnormal leads to the extremities, especially in case of an electrocardiogram suggesting an infarction in the anterior wall. In rare cases, however, one may see a normal 4th lead. Most often the opposite is the case.

Fig. 1 f. Shows interchange of all electrodes in clockwise direction. Likewise this electrocardiogram might on cursory inspection be taken to suggest an old infarction in the posterior wall. Also here, however, we see in Lead III no deep Q (but a small positive R), while at the same time P-QRS and T are all negative in Leads III and II.

In all these wrongly connected electrocardiograms we note that in the leads which show strikingly pathological excursions the P and T waves are negative, as likewise the chief deflection of the QRS complex. We ought always to think of a technical error when we see this phenomenon, and therefore also in case of an electrocardiogram suggestive of dextrocardia. The only normal electrocardiogram which shows negative P-QRS and T in one lead (the 3rd lead) is, as stated, the one we get in case of simple traverse position of the heart. If the electrode belonging to the left leg is placed on the right leg, this will involve no alteration of importance in the electrocardiogram, since the difference in potential between the left and the right leg is insignificant.

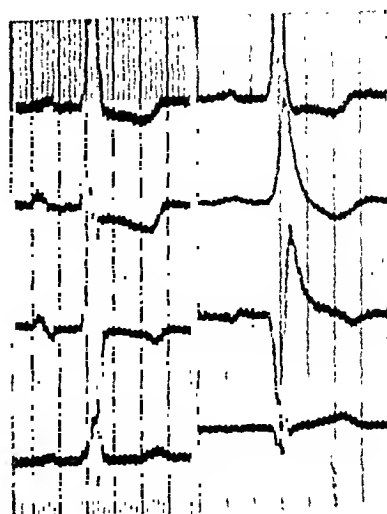
2. *Breach of lead.*

In our hospital we got some time ago some peculiar electrocardiograms from three patients with hypertension, who had previously shown the typical electrocardiograms of left ventricle hypertrophy (Fig. 2 a—Fig. 3 a and Fig. 4 a). All three of them had a blood pressure of about 200/130 and they had had typical attacks of angina pectoris before admission. One of these patients was subjectively free from symptoms and was about to be discharged. But a control electrocardiogram, taken just before he was to be discharged, seemed to indicate that he had got a fresh infarction of the posterior wall (Fig. 2 b). The electrocardiogram showed a deep Q and a high beginning of the S-T line in leads III and II, with corresponding depression of the S-T line in lead I, but with retention of the characteristic convexity seen in case of hypertrophy of the left ventricle. Thus it might seem to denote a fresh infarction of the posterior wall in a patient with hypertension, who had angina pectoris in the anamnesis. But this did not accord with the clinical picture at the moment. He was feeling quite well and was free from pain. It is true that cardiac infarction may, in purely exceptional cases, occur without pain, but all other symptoms of cardiac infarction were also absent (no leucocytosis, no fever etc.) Moreover, on closer inspection the electrocardiogram presented a rather strange appearance for one supposed to be due to posterior wall infarction. The QRS complex in the 3rd and especially in the 2nd lead had a peculiar straddling form. Besides, there could be seen a suggestion of a small R in the 3rd lead. Thus there was no deep Q in lead III, but a deep S.



a b
Correctly Lead to
coupled left leg
 broken

Fig.2.



a b
Correctly Lead to
coupled left leg
 broken

Fig.3

The situation was pretty soon made clear, when we also in the other two hypertension patients recorded similar infarction electrocardiograms (Fig. 3 b, 4 b). These latter two electrocardiograms were still more than the first suggestive of infarction in the posterior wall, as there was here seen a really deep Q in the 3rd lead. Just as in the first patient we had also here a high beginning of the S-T line in the 3rd (and 2nd) lead and a correspondingly depressed S-T line in the 1st lead. But also these two hypertension patients were subjectively free from symptoms and it was now evident that a technical error must have occurred.

First it was ascertained that the electrodes were correctly placed. The conducting wires were then examined and it was found that the wire leading to the left leg was broken.

The rupture was concealed by the insulating sheath, which was intact. The break explained why it was precisely the 3rd and 2nd leads that showed abnormality. We took control electrocardiograms of these three patients and now obtained quite ordinary ventricular hypertrophy electrocardiograms, such as we had previously recorded. In order now to prove that it was the break in the conduction that had occasioned the alterations, we again completely detached the connection to the left leg.

We then got once more the abnormal electrocardiogram indicative of infarction of the posterior wall.

In order to see the effect produced by breaking the connection to the right arm and left arm, we took the following electrocardiogram of one of these hypertension patients: Fig. 4 a shows the

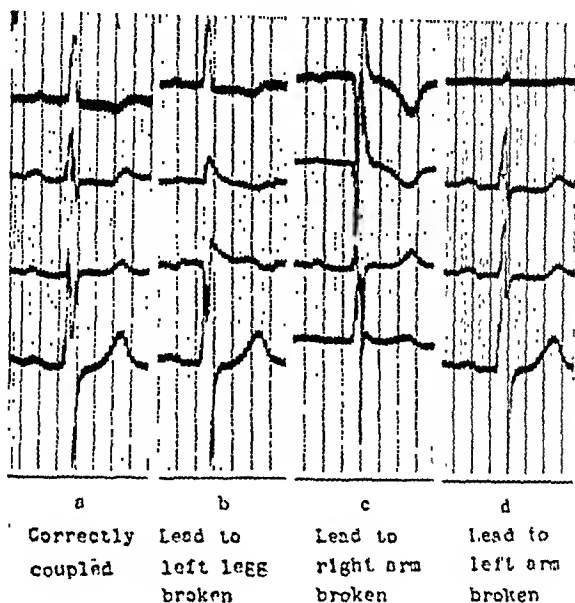
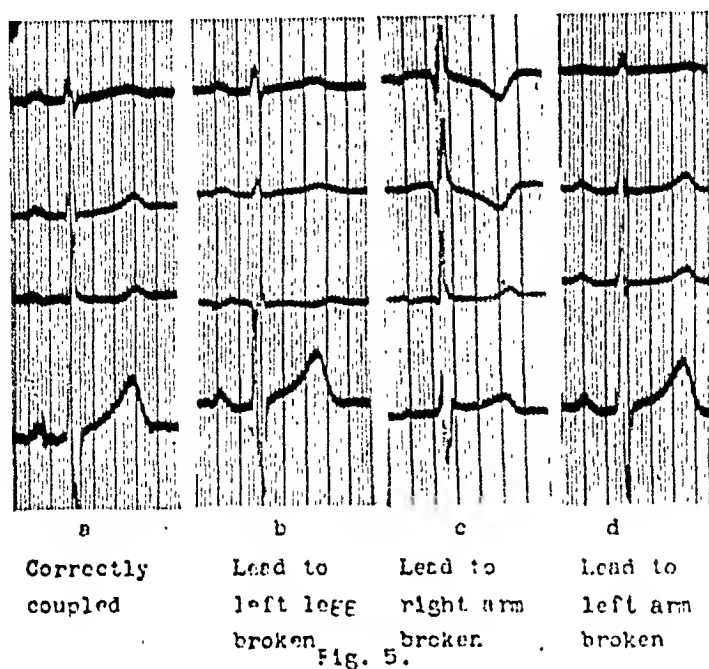


Fig. 4.

correct electrocardiogram, *i. e.*, without breach of connection, namely, a typical electrocardiogram of left ventricular hypertrophy. Fig. 4 b shows, as stated above, an ecg. taken when the connection to the left leg was broken. Fig. 4 c shows an electrocardiogram taken after breaking the conduction to the right arm. We here see a deep Q in leads I and II, as well as greatly inverted T waves in both leads. This electrocardiogram might illude us to regard it as indicative of an old infarction in the anterior wall. Fig. 4 d shows an electrocardiogram taken with interrupted connection to the left arm. Here we find no pronounced pathological appearance, only a featureless 1st lead and a slightly altered 3rd lead.

In order to see "broken-current electrocardiograms" from a normal heart the following electrocardiograms were taken: Fig. 5 a shows the correct electrocardiogram, *i. e.* without break

of connection, Fig. 5 b shows an electrocardiogram in which the lead to left arm is broken. We have here an somewhat deep Q in the 3rd lead but no high beginning of the S-T line, as was seen in hypertension patients. In Fig. 5 c the lead to the right arm is broken. This electrocardiogram may suggest an old infarction of



the anterior wall: deep Q and greatly inverted T' in the 1st and 2nd lead. The entirely normal 4th lead will speak against such a supposition. Moreover, in these cases with in reality normal hearts the absence of any record of angina pectoris in the anamnesis would be remarkable in such electrocardiograms suggestive of infarction. On detaching the lead to left arm (Fig. 5 d) no particular pathological change was observed.

We note that in case of rupture of one the electrodes just as in errors of coupling (interchange of electrodes), the deflections of the P and T waves, as well as the chief deflection of the QRS complex, are usually negative in the leads which are affected by the technical error. As already mentioned, this fact ought to arouse suspicion.

On rupture of the electrode to the left leg especially leads III and II will be affected, and rupture of the electrode to the right

arm will affect especially leads I, II and IV. On rupture of the electrode to the left arm we merely get a somewhat featureless 1st lead and a slightly altered 3rd lead, but no particular pathological changes.

The reason why these changes appear chiefly in pairs, respectively in the 2nd and third and in the 1st and 2nd leads, will be clear from inspection of Einthoven's triangle (Fig. 6).

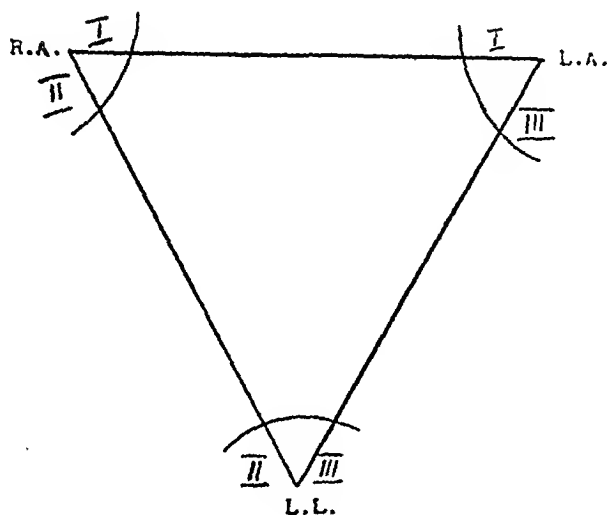


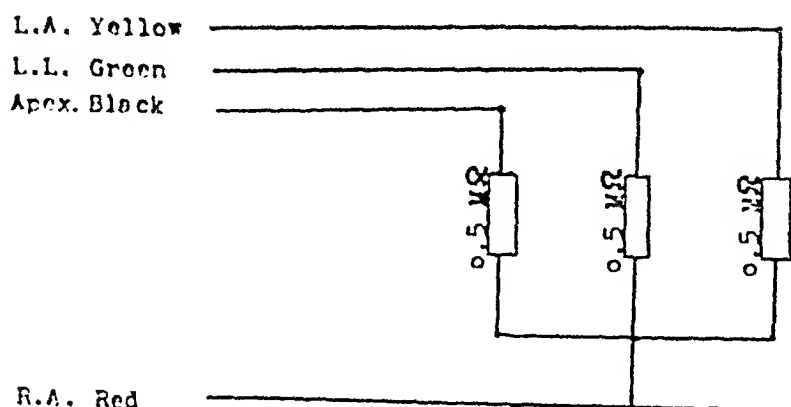
FIG. 6

In some cardiographs it will, on account of a different circuit arrangement we have in our apparatus (Elmqvist, Triplex), be impossible to record any electrocardiogram at all in case of breach of connection to the right arm, since the 1st and 2nd leads will then "go quite wild". Likewise, we cannot note any very marked changes in case of breach of connection to the left arm.

On interruption of a circuit one should expect that it would be impossible to obtain any electrocardiogram at all. Elmqvist has kindly explained to me how such peculiar electrocardiograms can nevertheless arise. The cause of the phenomenon is that capacitive influences may come into action from the other currents, as the amplifiers have a very high entrance impedance. The entrance grid of an amplifier with interruption of the incoming current has, as we know, no definite potential and it is left to chance to decide from which of the other currents the

tension will chiefly be conveyed. It is therefore very important to take care that there is good contact at the place from which we lead off. The alterations are most conspicuous when we use the disturbance-reducing electrode on the right leg.

By coupling in a resistance of about 500,000 ohms between each of the intakes for the currents to the left arm, left leg and apex cordis on the one hand, and the intake for the current to



Resistance placed inside in electrocardiograph.

Fig. 7.

the right arm, on the other hand (Fig. 7), the phenomenon can be eliminated. The reduction of entrance impedance which thus occurs has no influence in ordinary electrocardiography.

Summary.

The author deals with:

- 1) Coupling errors (interchange of the electrodes).
- 2) Breach of current (due either to failure to make contact at the leading-off place or to interruption of one of the leads).

The electrocardiograms obtained may in some cases resemble infarction electrocardiogram. Attention is especially drawn to the fact that in case of break of connection to the left leg there may be obtained electrocardiograms suggestive of infarction of the posterior wall in patients with left ventricle hypertrophy.

curves. Break of current to the right arm give electrocardiograms resembling those seen in case of anterior wall infarction, both in patients with left ventricle hypertrophy and in those with normal hearts.

The reason why "broken-current electrocardiograms" can occur at all is that the entrance grid of an amplifier with interruption of the incoming current has no definite potential, and capacitive influences may come into force from the other currents, when the amplifiers have a very high entrance impedance.

The phenomenon can be eliminated by coupling in a resistance of about 0.5 Megaohm between each of the intakes for the currents to the left arm, left leg and apex cordis on the one hand and the intake for the current to the right arm, on the other hand. The reduction of entrance impedance which thus occurs has no influence in ordinary electrocardiography.

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Variations in the Serum Proteins in Liver Diseases with Special Reference to their Diagnostic Significance.

By

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(Submitted for publication September 1, 1947.)

In an early attempt to determine the influence of diseases on the proteins of the blood Jolles (1902) by a crude method found the total protein including hemoglobin reduced in two cases of liver cirrhosis. Gilbert and Chiray (1907) showed that the total serum protein was lowered in 3 cases of cirrhosis with ascites, whereas Grenet (1907) found this also to be the case in cirrhosis without ascites. Fillinski (1925) claimed to have shown a globulin increase on cases of atrophic and biliary cirrhosis parallel to the degree of liver insufficiency, to the sacrifice of the serumalbumin and thought that this had diagnostic and prognostic significance. There are no analyses to support his assertions. The results of Starlinger and Winands (1928) on a larger material were so varying both in normal and in pathological cases where the A/G ratios could change from 0.4 to 2.4 in the course of a few hours, that one can hardly draw any conclusions as to the behaviour of the serum proteins in liver diseases from their results.

It was shown by Salvesen (1929) that characteristic changes in the plasma proteins were very common in diseases in which the liver was involved and that these changes were most pronounced in cases of Laënnec's cirrhosis, where low A/G ratios ranging between 0.30 and 0.89 were found, due both to decrease in albumin and in most cases increase in globulin. In one case of hepatosplenomegaly (probably subchronic hepatitis) a hyperproteinemia was demonstrated due to a large increase in the globulin.

It was pointed out that the diagnostic value of plasma protein determinations was uncertain, but the low A/G ratios found in Laënnec's cirrhosis were thought to be significant, although there were too few observations (11 cases) to justify the conclusion that a normal A/G ratio excludes cirrhosis. Abrami and Robert-Wallich (1929) obtained exactly the same results. In the interval since 1929 much work has been done on this field and the above mentioned observations have been confirmed,¹ but the question of the diagnostic value of plasma or serum protein determinations, where the nature of an existing liver enlargement is concerned, seems not to have been discussed on a larger, comparative material. This problem often meets the clinician and his results may be of major importance to the therapy. In connection with a chronic jaundice f. i. the differential diagnosis between hepatitis, tumor and choledochus-stone may be very difficult, especially in many of the cases of malignant hepatitis in middle-aged women, occurring during the occupation in Norway, with the irregular symptomatology with remissions and exacerbations and the often intense attacks of pain, which in several cases led us to perform laparotomy. It will be seen from our results, that especially in this disease are serum protein determinations of great value.

Another question is whether the serum protein changes in liver diseases are caused by a damaged liver function and as such may permit conclusions as to where the plasma proteins are manufactured as suggested by Salvesen (1929), or whether they exclusively are due to infection or malnutrition (Peters and Eisenman, 1933).

The present paper is our contribution to the discussion of the questions mentioned above, based upon our routine studies on the serum proteins for many years.

The Material.

In all the cases included in the material the diagnosis of the various conditions was regarded as established either by autopsy, liver biopsy, laparotomy and X-Ray examination, or because the clinical evidence seemed conclusive. The material includes:

¹ The results of Wiener and Wiener (1930) are very varying with an average normal A/G value of 2.70 and pathological values up to 20 and evidently cannot be compared with our own results. This also applies to the work of Tumen and Bockus (1937), in which an A/G value of 3.10 is considered normal and the A/G values in cirrhosis f. i. may jump from 0.50 to 1.54, down to 0.55 and up to 1.27 often in this course of only a few days.

Acute hepatitis: 24 cases, *hepatitis* ending fatally or turning chronic (malignant hepatitis): 25 cases. *Toxic hepatitis* (by medication) 5 cases, *cirrhosis*: 26, *splenomegalia thrombophlebitica*: 1 case. *Gall stone occlusion* with jaundice: 11 cases. *Cancer* of the bile ducts with jaundice: 17 cases, *gall stones* without jaundice: 9 cases. *Cancer hepatitis* without jaundice: 10 cases. *Carcinomatosis* and *sarkomatosis*: 7 cases. *Various other liver diseases*: 6 cases. *Hemolytic jaundice*: 7 cases. In all: 148 cases.

In the material is not included liver enlargement in heart diseases, leukemia a. s. f., where the serum protein determinations are of no significance to the diagnosis.

Methods.

Howe's method (1921) has been used in this clinic since 1924, with modifications introduced by one of us (H. A. S. 1926). In our first work the determinations were made on plasma, but in the present investigations serum was used and the blood drawn from patients in bed with only short stasis. Determination by the ultracentrifuge or electrophoresis is too elaborate and expensive to be used for routine work, so that the salting out method and Kjeldahl determinations have to be used. It has been held that by the Howe method there occurs some contamination of the albumin fraction by globulin and that the A/G ratios therefore by this method are higher than the real values (Bing & al. 1946, Björneboe 1943). We have no personal experience as to the accuracy of the electrophoretic method, but the results of investigators, who have compared the salting out and the electrophoretic method of Tiselius are somewhat confusing. Luetscher (1940) found about the same value for the A/G ratios in normals by the two methods, whereas in pathological cases the electrophoretic determinations constantly showed lower values for A/G than the Howe method. Malmros and Blix (1940) on the other hand found lower A/G by the salting out method (of Thorell) than by electrophoretic determination. Thygeson and Möller-Christensen (1946) conclude that the sodium sulfate method of Howe should be regarded as the standard method for fractional serum protein analyses.¹ The serum colour (icterus index) is determined with

¹ Many of the unexpected variations in the A/G ratios found in the papers of various investigators may be due to incomplete digestion of the total nitrogen, whereas the digestion of the albumin, containing sodium sulfate, is complete, giving to small values for the globulin, obtained by subtraction. That is the reason why Salvesen (1926) added potassium sulfate to the total protein digestion.

the Meulengracht method. Phosphatase values are given in Bodansky units.

Results.

Normal Values.

As our former determinations were made on plasma the normal material of Salvesen (1926) could not be used. There were only the results of Peters and Eisenman (1933) obtained from serum by the Howe method and we have therefore made a new series on normal persons, registered in table I, 14 males and 6 females for

Table I.
Normal Values of Serum Proteins.

No.	Name	Age	Total protein %	Albumin %	Globulin %	A/G
1	L. A.	25	6.46	4.79	1.85	2.59
2	P. S.	25	7.00	4.74	2.26	2.09
3	K. M.	26	7.25	4.75	2.50	1.90
4	O. A.	27	7.14	4.67	2.47	1.88
5	P. S.	28	7.30	4.76	2.54	1.88
6	T. G.	28	6.75	4.44	2.31	1.92
7	E. S.	29	7.62	4.92	2.70	1.82
8	E. O.	31	6.95	4.92	2.03	2.42
9	E. S.	32	7.29	4.36	2.93	1.49
10	R. H.	32	6.30	4.30	2.00	2.15
11	J. J.	32	7.14	4.63	2.54	1.82
12	S. H.	35	6.64	3.94	2.70	1.45
13	G. B.	45	7.44	4.77	2.67	1.78
14	R. H.	46	7.44	5.26	2.18	2.42
15	A. O.	24	6.99	4.55	2.44	1.87
16	K. M.	29	6.82	4.42	2.40	1.84
17	K. F. J.	38	6.11	3.90	2.21	1.77
18	L. L.	37	7.23	4.59	2.64	1.74
19	G. B.	40	6.85	4.29	2.56	1.67
20	S. N.	45	6.47	4.78	1.69	2.85
Average			6.96	4.59	2.37	1.97
Highest			7.62	4.92	2.93	2.85
Lowest			6.11	3.90	1.69	1.49

comparison with the values of Peters and Eisenman. These investigators found that the *total serum proteins* varied between 5.7 and 8 %, but only 4 were below 6.1 and 90 % between 6.3 and 7.7 %, the *albumin* varied between 4.1 and 6.1, but only one was over 5.5 %. The *globulin* ranged between 0.9 and 3 %, but

only one was below 1.4 % and 4 over 2.5 % (of 332 determinations). They therefore put the normal value of total protein to 6-8 %, albumin: 4-5.5 % and globulin: 1.4 to 3 %.

The twenty determinations of our own series all fall within the same limits and with less variations except that our lowest albumin is 3.90 % instead of 4 %. The A/G ratios vary between 2.85 and 1.49 with an average value of 1.97. Of the 20 determinations only 6 are above 2.00. A globulin > 3 % is considered pathologic, which is in accordance with the results of Bing (1940).

Acute Hepatitis.

In this group are listed cases suffering from a typical «icterus catharrhalis» and ending in complete recovery. There is only one biopsy, but the course of the disease, its relation to epidemic etc. characterise the disease as the classical commonplace hepatitis. The total protein was normal or even slightly raised in 20 cases,

Table II.
Acute Hepatitis.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata Formolgel	Serum colour	Phosphatase	Duration of icterus, weeks	Remarks
1	B. B. ♂ 21	1933 Nov. 20	7.46	3.56	3.90	0.91	+	50		12	Moderate jaundice.
2	A. A. ♂ 21	1934 Mar. 1 Mar. 14	6.61	3.89	2.72	1.43	+ ÷	45 7		2	Jaundice with fever. Abusus aethyl. Liver palpable.
3	A. A. ♀ 13	1936 Sept. 8 Oct. 20	5.12	2.03	3.09	0.66	+	150 30		8	Jaundice during epi- demic. Liver palp. Moderate ascites.
4	O. S. ♂ 38	1933 Nov. 10 1934 Jan. 2	6.25	3.11	3.14	0.96	÷ +	300 17		7 14	Diarrhea, fever and jaundice. Liver palpable.
5	A. E. ♀ 14	1933 Nov. 22	6.78	3.88	2.90	1.34	÷	18		2	Dyspepsia, fever and jaundice. Liver palpable.
6	R. R. ♂ 17	1938 Sept. 15 Sept. 28	7.36	4.17	3.19	1.30	÷	41 11		2	Moderate jaundice.

Table II. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Duration of icterus, weeks	Remarks
7	A. S. ♂ 36	1938 Jan. 24 Mar. 3	6.79	3.89	2.90	1.34	+		105 26		4	Jaundice with fever Liver palpable.
8	S. H. ♀ 18	1944 Feb. 14 Mar. 10	8.81 8.72	4.28 4.82	4.53 3.90	0.94 1.23	++	++	135 21	90	8	Oct. 1943 jaundice of short duration. Relapse medio Dec. Liver palpable.
9	O. H. ♂ 26	1944 June 12	7.49	3.99	3.50	1.14			37	5.6	2	Febrile jaundice.
10	I. M. ♀ 20	1944 Dec. 6 Dec. 14	6.89 7.61	3.32 3.84	3.57 3.77	0.93 1.02	++	++	90 18		2	Liver and spleen palpable.
11	H. Ö. ♂ 29	1945 June 27 July 3	7.64	4.10	3.54	1.16	++	++	75 14		5	Discharged from German conc. camp Apr. 30, 1945. Jaundice and fever May 20, 1945.
12	M. M. ♀ 50	Aug. 2	7.50	4.55	2.95	1.54	÷	÷	30	7.3	2	Moderate jaundice. Liver palpable.
13	K. W. ♂ 38	June 20	7.57	3.45	4.12	0.83	++	++	45		2	Fever and jaundice.
14	H. R. ♀ 26	1946 Mar. 2	8.39	4.11	4.28	0.96	++	++	13	5.2	1	Liver palpable.
15	S. N. ♂ 33	Feb. 13 Feb. 22	6.99 8.22	4.17 4.86	2.82 3.36	1.48 1.45	÷	÷	30 13	11.8 6.9	1	Liver palpable.
16	L. L. ♀ 60	June 20	6.93	2.92	4.01	0.72	÷	÷	13	8.2	4	Liver palpable.
17	L. O. ♀ 58	July 2 July 23 July 31	7.36 8.69 8.00	2.97 4.02 3.82	4.39 4.67 4.18	0.68 0.86 0.91	++ ++ ++	++ ++ ++	60 18	9.7	12	Moderate jaundice. Liver palpable.
18	E. H. ♂ 26	July 17	7.52	4.75	2.77	1.71	÷	÷	13	1.9	1	May 1946 jaundice in the tropics. Re- lapse in July.
19	K. M. ♂ 35	Sept. 16	7.60	4.29	3.31	1.29	÷	÷	30	2.7	1	Nauseated 1 month. Jaundice last week.

Table II. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Duration of icterus, weeks	Remarks
20	H. S. ♂ 38	1946 Sept. 19 Sept. 26 Oct. 8	6.41 6.12 6.06	2.34 2.35 2.90	4.07 3.77 3.10	0.57 0.62 0.93	÷ ÷ ÷	÷ ÷ ÷	45 60 7	17.9	3 4	Lymphogranuloma- tosis coli. Jaundice for 3 weeks, (inocula- tion?).
21	M. S. ♀ 48	1947 May 24 June 2	7.00	3.63	3.37	1.04	+	÷	19 12		12	Jaundice and fever March 1947. Re- lapse May 1. Col- oured feces. X-Ray: No concrement.
22	S. D. ♀ 68	1945 Nov. 20 Dec. 18 1946 Jan. 14	6.10 6.10 6.40	2.89 3.23	3.21 3.17	0.90 1.02	÷ ÷ ÷	÷ ÷ ÷	22 120 19	11.4 19.9		Operation for ulcer July 7, 1945. Blood- and plasma trans- fusions. Increasing jaundice since beg. Nov. 1945. Recov- ery.
23	M. N. ♀ 56	1946 Oct. 28 Nov. 5	7.34 7.13	3.44 3.34	3.90 3.79	0.88 0.80	++ ++	++ ++	41 17	19.6 9	3	Thyroidectomy and plasma transfusion 5 months prev. Biopsy.
24	A. L. ♂ 46	1947 Apr. 16 May 5	6.70 6.72	3.42 3.25	3.28 3.47	1.04 0.92	++ ++	++ ++	105 34		4 7	Resection for ulcer. Plasma transfusion 3 months before jaundice appeared.

except in case 3, where it was 5.12 %, due to a reduction of the albumin; in this patient, a girl of 13, there was also slight ascites. The A/G ratios were normal or slightly reduced in 11 cases (minimum 1.04) and below 1 in 13 cases with a lowest value of 0.57 in case 20. In this case the hepatitis was a complication to a malignant lymphogranulomatosis and should perhaps not have been included in the material, but the analyses show very clearly the influence of the hepatitis on the serum proteins with the rise in the A/G ratio as the jaundice disappears. The inverse proportionality between the icterus index and the A/G ratio is also seen from cases 8, 10 and 17. The lowered A/G ratio is in most cases caused by a reduction of the albumin and a rise in the globulin, but in some cases only by a rise in globulin. The last 3 cases were »return cases» and considered due to plasma or blood transfusions some months earlier.

*Hepatitis Ending Fatally or Developing into a
Chronic Stage.*

In table III are shown the findings in 24 cases observed clinically or privately by one of us (H. A. S.). They include what has been termed *malignant hepatitis* in Denmark and Norway, with 13 deaths. In 15 of them the diagnosis was confirmed by autopsy, biopsy or by laparotomy performed because of attacks of pain, simulating gall stone. Some of the patients are still alive with slight jaundice and palpable liver and spleen, some of them had a period of ascites demanding tapping (cases 17 and 19). We feel justified in including cases 12, 15, 19, 21, 22 and 24 in this group on account of the typical beginning during an epidemic and the characteristic course under constant control.

In all of the 24 cases, 63 determinations showed A/G ratios below 1, in some cases even below 0.30, with one exception in case 10, in which the serum protein values during a 6 months observation on April 27, deviated from the others, showing an A/G ratio of 1.16. This rise is probably real, as the patient's clinical condition varied and she was in a good period and apparently on the road to recovery when the determination was made, the serum colour being 14 and the S. R. 6, but then there was a relapse with intense jaundice (serum colour 225), the A/G fell to 0.66 and she died after laparotomy, during which biopsy of the liver was performed.

Case 15 is apparently going to recover after $1\frac{1}{2}$ years of illness. The jaundice has disappeared, the liver, which was considerably enlarged, is no more felt, but the serum protein values point to chronic damage of the liver. Case 19, an old lady, was suspected of cancer, although her jaundice started during an epidemic and no tumor could be found. She developed ascites, was tapped several times, but after 3 months this could be stopped, and her son who is a doctor, writes one year after, that she apparently is cured.

The low ratios are due both to a lowering of the albumin, which may go down to 1.45 %, but mostly to a rise in globulin. All of them had low albumin except once in case 20, when it was 4.12 %, but also here it dropped during the next examination. All of them had high globulin except case 10 on the first examination, when it was 2.94 %, but also here it rose to 3.96 %. But even in these two exceptions the A/G was below 1. The hyperglobulinemia

VARIATIONS IN SERUM PROTEINS.

Table III.

Hepatitis Ending Fatally or Turning Chronic (Malignant Hepatitis).

Table III.														
Hepatitis Ending Fatally or Turning Chronic (Malignant Hepatitis).														
No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	S.R. mm	Duration of icterus, weeks	Remarks	
1	B. L. ♀ 46	1941 Nov. 12 Nov. 19	5.91	1.86	4.05	0.46	+		195 180			4	Dyspepsia and icterus four weeks. Coma. Edema. Liver and spleen consid. enlarged. Mors. Autopsy.	
2	G. R. ♀ 55	1944 Sept. 13	6.27	2.41	3.86	0.68	+	+	330		4.2	4	Four weeks ago fever and jaundice. Coma. Liver and spleen enlarged. Mors. Autopsy.	
3	C. S. ♀ 83	1944 Oct. 17 Nov. 8	7.46 6.14	3.12 2.17	4.34 3.97	0.72 0.55	+	+	225 87		4.0 3.0	4 7	Jaundice four weeks. Liver enlarged, later smaller. Coma. Mors. Autopsy.	
	L. ♀ 7	1945 May 14	6.40	2.17	4.23	0.51	+	+	105		6.7	14	Jaundice and fever. Growing weakness. Liver and spleen enlarged. Mors. Autopsy.	
	H. B. ♀ 60	1945 Sept. 19	5.86	2.02	3.84	0.53	+	+	160		8.0	8	Jaundice and later coma. Liver palpable. Ascites. Mors. Autopsy.	
6	B. S. ♀ 48	1946 Oct. 7	6.41	2.52	3.89	0.63	+	+	105		4.3	2	Jaundice 2 weeks. Comatous on admission. Mors. Autopsy.	
7	S. O. ♀ 77	1943 July 7	6.14	2.58	3.56	0.73	+				15	22	Jaundice for 9 months. Enlarged liver and spleen. Mors. Autopsy.	
8	M. B. ♀ 48	1945 Dec. 7 Dec. 12 Dec. 18		7.71	0.87	6.84	0.12	+	+	60 37 45		40	26	Six months jaundice of varying intensity. For weeks consid. ascites. Large liver. Autopsy.

Table III. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata Formolgel	Serum colour	Phosphatase	S.R. mm	Duration of icterus weeks	Remarks
9	R. H. ♀ 52	1915 Oct. 17 Oct. 24 Nov. 7 Nov. 11 Dec. 12 1916 Feb. 7 Feb. 19 Mar. 13 June 5	10.85 9.76 9.85 10.59 11.67 11.30 10.92 9.31 5.89	2.58 2.34 2.17 2.22 2.00 2.19 2.16 2.18 1.76	8.27 7.42 7.68 8.37 9.67 9.11 8.86 7.16 4.13	0.31 0.32 0.28 0.27 0.20 0.24 0.23 0.30 0.42	÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷	105 105 60 90 22 30 30 37	5.0 117 107 110 124 122 121 125	18 18 52	Since June 45 jaundice of vary- ing intensity. Liver consid. en- larged. No ascites. Died after hematemesis. Au- topsy.	
10	M. M. ♀ 46	1914 Jan. 12 Feb. 2 Apr. 27 June 28 July 18	5.62 6.43 7.38 6.57 6.11	2.68 2.52 3.96 2.61 2.80	2.94 3.91 3.42 3.96 3.31	0.91 0.61 1.16 0.66 0.85	÷ ÷ ÷ ÷ ÷	150 60 14 225	14 20 6 5.1	11 28 6 11 54	Since June 43 jaundice of vari- able intensity. May 44 worse. Died July 18, 1914 after lapar- otomy. Partial autopsy.	
11	A. B. ♀ 60	1912 Apr. 27 June 1	9.15 8.11	2.79 2.39	6.36 5.72	0.41 0.42	÷ ÷	22 22		83 112	22	Jaundice during epidemic. Period- ic fever. Weil's Liver and spleen enlarged. Ascites. Died after 1 year.
12	U. B. ♀ 51	1914 Aug. 23	7.06	1.89	5.17	0.37		60		32	30	Febrile enteritis with jaundice Jan. 44. Died Apr. 1915 after a period of increas- ing ascites.
13	R. C. ♀ 49	1915 Nov. 12	7.17	2.88	4.29	0.67		75			35	Jaundice March 45. Laparotomy Aug. 45 (hep- atitis). Died May 12, 1916.
14	R. B. ♀ 60	1914 Sept. 30	8.12	1.67	6.45	0.26		98		45	35	Jaundice May 1914, fever, glo- sitis, ascites. Died Oct. 6 1914. Par- tial autopsy.
15	O. H. ♀ 59	1915 Aug. 4 Sept. 9 Dec. 18 1916 Feb. 12 Mar. 26 May 14 Aug. 6	8.71 7.99 7.52 8.49 7.03 9.02 8.67	2.46 2.51 3.09 3.82 3.40 3.68 3.57	6.25 5.48 4.43 4.67 3.63 5.34 5.10	0.39 0.16 0.70 0.82 0.93 0.68 0.70	÷ ÷ ÷ ÷ ÷ ÷ ÷	80 30 11 7 6	5.1 6.1 62	49 82 76 62	12	Jan. 1915 dyspep- sia. In May jaun- dice, enlargement of liver, which later disap- peared. Clinically symptom free Aug. 1916.

Table III. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	S.R. mm	Duration of icterus weeks	Remarks
16	H. H. ♂ 53	1946 Mar. 25 Apr. 3 Apr. 29	6.63 6.71	2.78 3.04	3.85 3.67	0.73 0.82	++ ++	++ ++	60 34 15	7.7 9.9	36 39 36	40	Since June 45 jaundice of vary- ing intensity. Liver and spleen enlarged. No as- cites.
17	K. E. ♀ 46	1946 Mar. 3 Apr. 2 Apr. 16 June 13 Sept. 25 1947 Jan. 16 Mar. 4	8.10 8.15 8.10 8.36 7.50 8.81 7.21	2.40 2.32 2.37 2.50 2.76 2.86 2.24	5.70 5.83 5.73 5.86 4.74 5.95 4.97	0.42 0.40 0.41 0.42 0.58 0.48 0.48	++ ++ ++ ++ ++ ++ ++	++ ++ ++ ++ ++ ++ ++	30 18 60 11 26	18 18.5	142 121	3 yrs	For 3 years jaun- dice of varying intensity and pe- riods of fever. Large liver and spleen. Ascites. Biopsy.
18	M.F.S. ♀ 52	1944 July 7 Aug. 3 1945 Apr. 7 May 30 Nov. 8 1946 Feb. 25 June 8 Dec. 8	7.04 7.45 8.60 6.86 7.19 7.42 7.22 7.17	3.18 3.23 2.88 1.45 2.26 3.02 3.11 2.89	3.86 4.22 5.72 5.41 4.93 4.40 4.11 4.28	0.82 0.77 0.51 0.28 0.46 0.69 0.76 0.67	++ ++ ++ ++ ++ ++ ++ ++	++ ++ ++ ++ ++ ++ ++ ++	67 52 90 90 60 13	16.5	2 19 19 34 34 25	2 4 37 52	Since June 44 jaundice of vary- ing intensity, liv- er enlarged, later not palpable. Jaundice disapp. Feb. 1945. At one time moderate ascites. Biopsy.
19	R. F. ♀ 78	1945 July 7	7.77	2.17	5.60	0.30	++	++	90	21.5	52	26	Jaundice during epidemic. Asci- tes, which disapp. Cured? after 1 year.
20	N. G. ♀ 37	1945 July 25 1946 Nov. 25	9.54 9.25	4.12 3.45	5.42 5.75	0.76 0.60	++ ++	++ ++	14 45	30.5 8.25	87 117	3?	One year grey stools. Since July jaundice. Consid. liver enlarg. Spleen palp. 1946 increas. of jaun- dice. Biopsy.
21	O. E. ♀ 17	1945 Feb. 26 Mar. 14	6.39 6.47	2.50 2.76	3.89 3.71	0.64 0.74	++ ++	++ ++	45 30	11	13 21	29 31	Varying jaundice for more than 1/2 year.
22	K. K. ♂ 15	1942 Mar. 13 June 6 July 7	7.41 6.81 8.24	3.47 3.10 3.38	3.94 3.71 4.86	0.88 0.84 0.70	÷ ÷ ÷	÷ ÷ ÷	270 180 24		51 40 110	21 33 38	Jaundice during epidemic. Liver and spleen en- larged.

Table III. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	$\frac{A}{G}$	Takata	Formolgel	Serum colour	Phosphatase	S.R. mm	Duration of icterus, weeks	Remarks
23	K.W. ♂, 26	1946 July 1 July 15	11.06 10.00	2.90 3.85	8.16 6.15	0.35 0.62	+	+	45	20.2	55	18 20	Jaundice following diarrhea during epidemic. Bi- opsy.
24	O. S. ♂, 42	1939 June 3	5.62	2.31	3.31	0.73	+		187		28	21	Jaundice during epidemic. Liver enlarged.

might reach 9 %, the result being a *hyperproteinemia* in 9 of the 24 cases, with a maximum value of 11.67 % in case 9.

In table IV is recorded the findings in a case of infectious hepatitis with somewhat unusual features. She was a young woman, 17 years of age, when she entered the clinic on March 23, 1943. She had been under constant control after a slight tuberculous infection 4 years previously and for nearly 2 years had been in full work with *constantly increased S. R.* up to 100 mm without any other symptoms except loose stools for half a year. A month after she had had to nurse her mistress during an attack of jaundice, she was taken ill with fever and pain in the left side of the abdomen and when she entered the clinic she had a slight jaundice (icterus index 30), but without fever. There was found a hyperproteinemia of 9.38 %, due to a rise in globulin ($A/G = 0.62$). She stayed in the hospital for 5 weeks and the hyperglobulinemia continued after the discharge. She was admitted again on Sept. 18 after a month in bed with sore throat and swollen glands in the neck, during which the jaundice returned. She stayed now for 8 months with enlarged liver and spleen, had an intense glossitis and cheilitis, various infections of skin and different glands with abscess formation. The jaundice varied with a serum colour up to 45 and the hyperproteinemia reached a maximum of over 12 % with $A/G = 0.17$; more than 10 % of globulin. After a protracted course the jaundice disappeared, the infection ceased, liver and spleen became impalpable, the serum protein became nearly normal. She now feels well and can do some work, but the sedimentation rate is still high and variable. The pronounced anemia also disappeared. The peculiar electro-

Table IV.

A Case of Infectious Hepatitis with Unusual Features.

B. N. 19 years.

Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	S.R.	Serum iron.
1943										
Apr. 4	9.38	3.58	5.80	0.62	+	+	14	10.6	82	
Apr. 19	9.71	3.74	5.97	0.62						
Apr. 27	9.90	3.64	6.26	0.58	+	+	14		90	
May 27	11.84	3.53	8.31	0.43					133	
Sept. 23	12.20	3.00	9.20	0.33	+	+	30		148	
Oct. 10	12.29	2.44	9.84	0.25			45		150	56
Nov. 10							16			
Dec. 7										82
Dec. 16	12.01	1.71	10.30	0.17	+	+	38			
1944										
Jan. 25	10.60	2.44	8.16	0.30						
Feb. 19	10.62	2.20	8.42	0.26						
Feb. 24	10.37	2.61	7.76	0.34						
Mar. 4					+	+	4		160	
Apr. 19	10.68	3.24	7.44	0.44						
May 17	9.80	3.05	6.75	0.45	+	+	5		152	
Nov. 24	9.93	4.19	5.74	0.73	+	+	4		72	
1945										
Sept. 10	8.36	4.32	4.04	1.07	+	+			36	
1946										
Oct. 16	9.00	4.17	4.83	0.86	+	+	4		60	

lytic changes in the patient's serum have been mentioned by Broch (1945). The serum proteins had an isoelectric point of 7.40.

Toxic Hepatitis (by Medication).

In table V are found the analyses in 5 cases of hepatitis caused by medication including a case of acute yellow atrophy of the liver after Cinchophen. In the first 3 cases the serum proteins are normal but in the last 2 cases, the A/G ratios are lowered and in the fatal case it goes down to 0.59.

Cirrhosis of the Liver.

Of the 26 cases in table VI, 12 are anatomically controlled by autopsy, biopsy or during laparotomy. Of the remaining 14 cases, 4 had varices of the oesophagus besides having a characteristic history and clinical picture. Three others had chronic alcoholism

Table V.
Toxic Hepatitis (by Medication).

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata Formolgel	Serum colour	Phosphatase	Duration of jaundice, weeks	Remarks
1	K. L. ♂ 25	1937 Apr. 22 May 13	6.91	3.87	2.71	1.42	+	105 23		1	Inc. prim. Jan. 1937 Twenty injections of Neosalvarsan. Jaundice Apr. 17. Liver palp.
2	E. P. ♂ 65	1940 Mar. 26 Apr. 7	6.11	3.77	2.31	1.51	+	45	18.3	2	Jaundice after 5 in- jections of Neo- salvarsan. Liver palp.
3	R. L. ♀ 46	1946 June 22 June 27	6.73	4.07	2.66	1.52		45 11	1.6	1/2	Jaundice 3 days after use of extract. filicis for helmin- thiasis
4	K. P. ♂ 26	July 26 July 29	9.55 7.90	4.32 3.83	5.23 4.07	0.82 0.96	— +	14	5.0	1	Jaundice after use of Sulfathiazol for urethritis gonorrh. Lasted 14 days. Biopsy.
5	H. W. ♀ 67	1936 Jan. 8	6.14	2.29	3.85	0.59	+	150		3	Jaundice after use of Cinchophen for ar- thritis. Autopsy: Acute yel- low atrophy.

in the history. In all of the cases the A/G ratios were below 1, in most of them far below this value, down to 0.17, but in two of the cases (1 and 10) they were unexpectedly high in view of earlier findings. These two were not anatomically controlled. The tendency to high total protein values were present in some of the cases, but there are also values down to 5.45 and 4.26 % due to low albumin values. In case 9 the liver cirrhosis confirmed by autopsy, developed during 3 years as a complication to a myxedema. There is a steady fall of the A/G from 0.98 to 0.69. In other cases the time factor had no characteristic influence.

If we take only the anatomically controlled cases (9, 11, 14, 16, 19, 20, 21, 22, 23, 24, 25 and 26) the A/G ratios ranged between 0.87 and 0.07 not counting the first observation in case 9 three years before the development of the cirrhosis. If we add 3

Table VI.
Cirrhosis Hepatis.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	$\frac{A}{G}$	Takata	Formolgel	Serum colour	Phosphatase	Remarks
1	F. I. ♀ 36	1929 Mar. 25	7.65	3.82	3.83	0.99			15		1920 lues. Last few months ascites. Large spleen. Edema. WR ÷.
2	K. B. ♂ 38	Mar. 3	6.34	2.69	3.65	0.74					Jaundice. Hematemesis. Ascites. Edema. Large liver. Alcoholism.
3	A. I. ♂ 31	1931 June 26	7.24	3.00	4.24	0.71			15		Ascites, large spleen, urobilinuria.
4	H. B. ♂ 43	Oct. 7	7.53	3.05	4.48	0.68					Chron. alcoholism. Large liver. Urobilinuria.
5	O. G. ♂ 36	1933 Oct. 28	8.19	2.88	5.14	0.56	+		4		Eight years ago jaundice during epidemic. Now ascites, edema, large liver. Anemia.
6	H. L. ♂ 65	1935 Dec. 19	8.22	1.15	5.59	0.17	+		22		Lues 1911. Ascites. Edema. Large liver. WR ÷. Chron. alcoholism.
7	G. H. ♀ 28	1936 Nov. 24	7.43	3.28	3.87	0.85	+		4	2.75	Ascites. Large liver and spleen. Urobilinuria. Anemia.
8	K. B. ♂ 63	1937 Mar. 9	7.41	2.48	4.93	0.50	+		8		Dec. 1935 jaundice, now ascites. Urobilinuria.
9	G. P. ♀ 54	1937 Mar. 8 Apr. 15 1940 Aug. 15 Oct. 14	9.01 7.11 7.22 6.71	4.17 3.31 3.06 2.74	4.51 3.80 4.16 3.97	0.98 0.87 0.74 0.69			6 8 13.5 8	4.5	Started 1937 with myxedema and anemia. 1940 liver and spleen much enlarged. Ascites. Varic. oesophagi. Autopsy.
10	O. B. ♂ 61	1939 June 15	5.77	2.80	2.97	0.94			5.5		Four years ago jaundice, later 2 relapses. Hematemesis, ascites. Varic. oesophag. Large liver.

Table VI. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
11	H. J. ♀ 60	1940 Sept. 9	6.26	2.58	3.68	0.68	+		5		Hematemesis, large liver, varic. oesophag. Autopsy.
12	O. L. ♂ 46	Dec. 12	5.80	2.52	3.28	0.64	+		10		Chron. alcoholism. Lucs. Large liver and spleen. Ascites. Varic. oesophag.
13	T. S. ♀ 40	1941 Mar. 19	6.10	2.32	3.78	0.62	÷		7		1941 consid. ascites and hepato-splenomegaly. March 1942 jaundice and abdominal pain. Slight edema.
		1942 Oct. 14	5.86	2.43	3.43	0.71	+		15		
		1943 May 13	6.32	2.46	3.86	0.64	+	+	18	4.4	
14	I. J. ♀ 43	1942 Jan. 28	5.70	2.28	3.42	0.67	÷		11		Five years ascites with frequent tapping. Hepato-splenomegaly. Varic. oesoph. Splenectomy.
		Feb. 18	5.88	2.54	3.34	0.76					
		1943 Mar. 26	5.76	2.43	3.33	0.73					
		May 24	6.77	3.14	3.63	0.87					
		1944 Mar. 10	6.25	2.60	3.65	0.71	+	+	7	19.3	
		Apr. 4	6.38	2.60	3.78	0.68					
		Apr. 19	Splenectomy								
		May 2	5.90	2.22	3.68	0.60	+	+	16		
		June 9	6.50	2.81	3.69	0.76			9		
15	B. B. ♀ 43	1943 Apr. 16	7.49	3.21	4.28	0.74	+				Four years ago resection ventriculi. Later periodic jaundice; liver and spleen enlarged.
		May 3	7.54	3.28	4.26	0.77	+	+	45	26.4	
16	S. W. ♀ 55	1943 Sept. 9	6.30	2.58	3.72	0.69	+	+	30	18	For 2½ years jaundice of varying intensity. Consid. hepato-splenomegaly. No ascites. Autopsy.
		1944 Jan. 18	5.41	2.30	3.11	0.74	+	+	24		
		1945 Feb. 28	5.82	2.47	3.35	0.74			45		
		June 11	4.26	1.91	2.35	0.81				8.1	
		Dec. 29	6.71	1.51	5.20	0.29					
17	A. G. ♀ 68	1944 Apr. 18	6.70	3.03	3.67	0.82	+	+	7	1.7	Abdominal pains. Hepato-splenomegaly. Varic. oesoph. Moderate edema.
18	A. A. ♀ 20	May 30	7.76	2.35	5.41	0.43	+		13		Since 1939 periods of jaundice. Hepato-splenomegaly. Varic. oesoph. Died.

Table VI. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
19	S. H. ♀ 32	Oct. 27 Nov. 8 1945 Oct. 11 Nov. 20	7.12 8.00 10.0 8.48	2.46 3.11 2.90 2.54	4.66 5.59 7.10 5.94	0.53 0.74 0.41 0.43	+	+	17 10.5 45 60	16.9	Four years ago slight jaundice. Later periodic. jaundice, hematemesis. Hepato-splenomegaly. Varic. oesoph. Biopsy.
20	G. F. ♀ 19	1945 Jan. 1	7.29	2.27	5.02	0.45	÷	+	5	4	For 2 years ascites and large spleen. WR +. Specif. treatment. Autopsy.
21	T. B. ♂ 75	Dec. 12	5.45	2.16	2.99	0.82					Edema and ascites for 1 year. No jaundice. Autopsy.
22	E. R. ♂ 46	1946 Feb. 19	5.15	1.89	3.56	0.50	+	+	22	5.2	One and a half years ago WR +. Intense specif. treatment. For 6 weeks increasing ascites. WR +. Autopsy.
23	K. H. ♂ 61	1946 Sept. 13 Sept. 23	7.63 6.92	2.67 2.68	4.96 4.24	0.54 0.62	+	+	7	5.2	Dyspepsia 5 years. Hematemesis. Mod. hepato-splenomegaly. Biopsy.
24	R. F. ♀ 50	1946 May 7 May 21	7.85 6.62	1.34 0.42	6.51 6.20	0.20 0.07	+	+	37 30	8.25	Four months jaundice. Ascites. Edema. Large liver. Laparoscopy. Tapped May 10.
25	A. H. ♂ 66	1946 Feb. 5	7.57	2.57	5.00	0.51					For 3 months diarrhea. Enlarged liver, development of ascites, glossit. Died March 3, 1946. Partial autopsy.
26	K. J. ♂ 44	1947 Mar. 15	6.21	2.63	3.58	0.73	+	+	8		Lues 1943. Cirrhosis discov. during operation for ulcer Feb. 1947. WR ÷. Ascites. Biopsy.

postmortem cases from Salvesen's first material (1929) in which the A/G ratios ranged between 0.30 and 0.63, we have a material of 17 cases of manifest cirrhosis with ratios between 0.87 and 0.07.

Table VII.

A Case of Splenomegalia Thrombophlebitica Developing into Cirrhosis.
L. E. male, born Oct. 28, 1897.

Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
1937 Feb. 11 1942	6.91	3.77	3.14	1.20	÷		6		Since 1925 repeatedly blood vomiting. Enlarged liver and spleen. Varic. oesophag. Laparotomy. Dec. 12, 1946. Biopsy: cirrhosis.
Mar. 10 1943	6.35	3.35	3.00	1.11	÷		15		
Jan. 18 1946	6.38	3.25	3.13	1.04	÷		17		
Oct. 23 1947	6.69	2.85	3.84	0.75			17	4.45	
Jan. 8	6.00	2.55	3.45	0.74	÷	÷			
Jan. 29	5.70	2.57	3.13	0.82	+		10		

In table VII are recorded the findings in a case of splenomegalia thrombophlebitica developing into cirrhosis during a 10 years observation with the same characteristic findings, when the cirrhosis is manifest.

Table VIII.

Gall Stone Occlusion with Icterus and Two Cases of Cholangitic Cirrhosis, in Which Removal of Gall Stones had no Effect.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	Duration of jaundice, weeks	Remarks
1	T. V. ♂ 64	1939 Feb. 23	6.93	3.91	3.02	1.26	÷		30		8	Many characteristic attacks. X-Ray: gallstones.
2	B. H. ♀ 54	1943 June 25	6.85	3.70	3.15	1.16	÷		13	14.6	14	Many characteristic attacks.
3	G. S. ♂ 60	1943 Apr. 10 1944 Aug. 25 Oct. 11 1945 June 8	7.30 6.64	4.08 3.98	3.22 2.66	1.23 1.50	÷ ÷		5 17	9.35 6.3		Repeated attacks of cholelithiasis with fever. Operation Sept. 20, 1943. New attacks with jaundice.
4	S. B. ♂ 49	1944 Jan. 19	7.25	4.56	2.69	1.70	÷	÷	37	27	52	Repeated attacks Operation.

Table VIII. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Duration of jaundice, weeks	Remarks
5	M. L. ♀ 46	1944 Mar. 23 1945 Oct. 30 Nov. 13 Nov. 20	6.80 6.81 6.35	4.34 3.99 3.35	2.46 2.82 3.00	1.76 1.41 1.12		÷ ÷ ÷	30 43 45	8.6	4	Mb. Cushing. Oct. 25, 1945 attack of cholelithiasis with jaundice. Operation Nov. 19, 1945.
6	T. S. ♂ 40	1945 Feb. 16 Feb. 19 Mar. 24 June 8 July 23 1946 Apr. 4	6.51 6.74 7.00 7.50 Operation 6.55	3.88 3.88 3.96 4.40 Operation 4.38	2.63 2.86 4.04 3.10 Operation 2.17	1.48 1.36 0.98 1.42 Operation 2.02	÷ ÷ ÷ ÷ Operation ÷	÷ ÷ ÷ ÷ Operation ÷	45 22 22	5.6	39 56	Repeated attacks of cholelithiasis. For 9 months constant jaundice of varying intensity. Successful operation.
7	B. W. ♀ 52	1945 Nov. 27 Dec. 3	6.53	3.32	3.21	1.03			23 7	7.6	1	Diabetes. Jaundice for one week after an attack.
8	M. K. ♂ 63	1946 Feb. 21	6.71	3.46	3.25	1.06	÷	÷	68	42.5	14	For 2 years frequent attacks with jaundice. Operation.
9	J. A. ♂ 56	1947 Apr. 18	7.12	3.76	3.36	1.12	+	÷	90		4	Since Sept. 46 periods of fever and jaundice. Operation.
10	I. E. ♀ 31	1945 Oct. 25 1946 Jan. 29	7.00 7.02	3.29 3.80	3.71 3.22	0.89 1.18	÷ ÷	÷ ÷	240 225	15.9	104	Frequent typical attacks since 1937. Const. jaundice since 1943. Operation March 44 and Apr. 45. Large liver and spleen. Biliary cirrhosis. Died June 47.
11	E. D. ♀ 56	1946 Feb. 14 1947 Jan. 23 Jan. 29 Feb. 25 Mar. 9 Apr. 11 May 5 May 30 June 13	7.51 6.83 7.14 6.99 7.14 5.72 6.11 5.72 6.01	3.34 2.66 2.88 3.02 2.56 1.96 2.07 1.01 1.83	3.97 4.17 4.26 3.97 4.58 3.76 4.04 4.71 4.18	0.89 0.63 0.67 0.76 0.56 0.52 0.53 0.21 0.43	÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷	÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷ ÷	105 135 135 98 105 112 120	32.2	116	From 1925 to 35 frequent attacks of cholelithiasis without jaundice. Since Nov. 43 const. jaundice. Operation 1944. No effect on jaundice. Large liver and spleen. Biopsy: Gall. stasis with consid. cirrhosis. Tapping of ascites since April 47. Died July 9. Autopsy.

Gall Stone Occlusion with Jaundice.

The findings in the 11 cases are seen on table VIII. Most of them were severe cases with long standing jaundice of varying intensity, in 8 of them the diagnosis was verified by operation (in 1 case also by autopsy), in 1 by X-ray; for cases 2 and 7 there was no such confirmation of the clinical diagnosis, but the symptoms were typical. In all of the patients except 3 are seen changes in the serum proteins with some lowering of the A/G ratios, but only in the last 2 cases in which cholangitic cirrhosis developed did the A/G ratio go below 0.98. In these two cases lasting nearly 4 years, operation with removal of gall stones had no effect. In case 10 the A/G rose from 0.89 to 1.18 after correction of existing anemia and K-vitamin deficiency, but in case 11 the A/G value fell to 0.21 during the 1½ years she was under observation.

Gall Stone without Jaundice.

These observations, recorded in table IX are included in order to show that gall stone disease even with frequent attacks, but without biliary stasis, has almost no influence on the serum proteins.

Obstructive Jaundice due to Cancer or Swollen Lymph Glands.

There are 17 patients in this group, listed on table X, of which 16 suffered from cancer and 1 from calcareous glands in porta hepatis. It is seen that all of the patients have considerable changes in their serum proteins. The albumin is always lowered, and this seems to be the chief factor in the production of the low A/G ratios, although there also occurs some rise in the globulin. There is consequently hypoproteinemia in 6 of the cases, but of 28 determinations the A/G ratio is still above 1 in 17 and between 1 and 0.90 in the rest except once in case 11 with edema and ascites, when it was 0.83. The effect of radical operation for cancer pap. Vateri is seen in case 10, where the T. P., the albumin and the A/G steadily rose to normal values.

It is interesting to compare this case to case 11, table VIII. Both patients had cirrhosis (biopsy), but in the first patient only as a consequence of pure bile stasis, due to cancer, in the other the cirrhosis apparently was of cholangitic (inflammatory)

Table IX.
Gall Stone without Jaundice.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
1	K. B. ♂ 47-50	1938 May 12	7.15	3.97	3.18	1.25					Since Jan. 1937 dyspeptic trouble. March 13 violent attack. X-Ray: no contrast in gallbladder.
2	E. E. ♂ 54	1944 Oct. 30	6.29	4.03	2.26	1.79	÷ ÷	7	0.6		Since 1935 repeated attacks of cholelithiasis. Operation.
3	A. F. ♀ 50	1945 Oct. 1	6.50	3.74	2.76	1.36	÷ ÷	8	3.5		Repeated attacks of cholelithiasis. Diabetes.
4	B. L. ♀ 49	1946 Jan. 31	6.48	4.31	2.17	1.90	÷ ÷	5	4.3		For 5 years characteristic attacks. Operation.
5	A. B. ♀ 32	1945 Apr. 9	6.79	4.35	2.44	1.80	÷ ÷	4			Repeated attacks. Operation.
6	A. S. ♂ 71	Mar. 7	6.73	3.78	2.95	1.28		8	9.5		Characteristic attacks since 1925. Operation.
7	M. L. ♀ 37	1946 May 8	7.00	4.33	2.67	1.62	÷ ÷	5	1.1		Repeated attacks. X-Ray: Stones.
8	A. P. ♀ 61	Nov. 29	7.01	4.24	2.77	1.53	÷ ÷	6	2.0		Dyspeptic trouble for 14 years. X-Ray: Gallstone.
9	O. H. ♀ 59	Aug. 2	7.05	4.23	2.87	1.50	÷ ÷	10			Last years repeated attacks. Operation.

origin and the action on the serum protein was much more pronounced.

Cancer Hepatis.
In 10 cases (table XI) suffering from cancer hepatis without obstruction of the common bile duct, 8 were controlled by autopsy, while the remaining 2 had characteristic findings over the liver

Table X.

Icterus due to Stenosis of the Bile Ducts Caused by Cancer and Lymphadenitis.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphatase	Duration of jaundice, weeks	Remarks
1	H. O. ♀ 61	1938 Mar. 3	4.75	2.39	2.36	1.01			135		32	Ca. pancreatis. Ascites. Autopsy.
2	J. U. ♀ 67	1942 Mar. 14	7.96	3.90	4.06	0.96	÷		210		4	Ca. vesic. felleae with bile stasis. Metastatic invol. of many organs. Autopsy.
3	H. H. ♂ 62	1943 July 13 Aug. 14 Sept. 10	4.85 5.92 6.94	2.49 2.86 3.68	2.36 3.06 3.26	1.05 0.93 1.13	÷ ÷	÷	180 30 16	35 40	16 20	Ca. papill. Vateri. Jaundice of varying intensity. Laparotomy Oct. 9 1943.
4	S. L. ♂ 45 46	1943 June 12 June 17 July 29	7.25	3.57	3.68	0.97	÷	÷	195 225 225	132 100 75	12	Ca. duct. choled. Jaundice of varying intensity. Radical operation.
5	R. N. ♂ 50	1944 Aug. 10	7.04	3.36	3.68	0.91	÷	÷ +	195	19	20	Ca. duct. hepat. Laparotomy (inoperable).
6	D. P. ♀ 38	1942 May 29	6.20	3.20	3.00	1.06	÷		150		20	Ca. pancreatis. Constant jaundice. Operation. Liver-biopsy: bile stasis.
7	H. S. ♀ 44	1944 Oct. 23	6.38	3.04	3.34	0.91	÷	÷	135	18	12	Ca. pancreatis. Operation (palliat.)
8	M. B. ♀ 62	1945 Feb. 16	6.04	3.24	2.90	1.16	+	÷	135		8	Ca. pancreatis. Laparotomy.
9	S. E. ♂ 55	1945 June 19	6.44	3.11	3.33	0.94	+	÷ ÷	105	49	52	Ca. papill. Vateri. Jaundice 1943, but constant only 1 year. Autopsy. Liver degeneration.
10	S. S. ♀ 40	1946 Jan. 7 Jan. 17 Feb. 14 Apr. 5 May 14 Aug. 7 Dec. 17	6.82 6.64 6.64 Operation 6.13 7.49 7.29	3.45 3.55 3.55 3.53 4.50 4.74	3.37 3.09 2.60 2.99 2.55	1.02 1.10 1.39 1.50 1.85	÷ ÷ ÷ ÷ ÷	÷ ÷ ÷ ÷ ÷	90 225 270 9 5 6	13 8 11 10	4 9	Ca. papill. Vateri. Constant jaundice. Radical operation. Liver biopsy: biliary cirrhosis.

Table X. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Duration of jaundice, weeks	Remarks
11	O. K. ♂ 65	1946 Aug. 28 Sept. 2	5.72 5.21	2.60 2.55	3.12 2.66	0.83 0.96	÷ ÷	÷ ÷	53 150	17	12	Ca. coli with metast. Edema. Ascites. Liver biopsy: Ca. nodules.
12	H. B. ♀ 70	Apr. 4	5.41	2.67	2.74	0.97	÷	÷	150	6	10	Ca. hepatitis of unknown origin. Jaundice. Edema. Laparotomy and biopsy.
13	J. H. ♂ 44	Aug. 21 Aug. 24 Sept. 3 Sept. 18	6.40 6.87 6.40	3.30 3.56 3.16	3.10 3.31 3.24	1.06 1.07 0.97			30 83 90	34 35	4	Aortit. luetic. and ca. ventriculi with metast. to lymph glands. Biopsy.
14	H. A. ♂ 68	Nov. 8 Nov. 23 Dec. 10	6.46 6.70	3.32 3.53	3.14 3.17	1.06 1.11	÷ ÷	÷ ÷	75 30 105	10.7	16	Jaundice of varying intensity. Opera- tion: Ca. pancrea- tis?
15	O. M. ♀ 52	Nov. 9 Nov. 26 Dec. 5	6.48 5.49	3.29 2.72	3.19 2.77	1.03 0.98	÷ ÷	÷ ÷	120 225	18	10	Sept. 1944 op. for ca. ventric. For 10 weeks jaundice with palp. liver and en- larged gall bladder.
16	O. S. ♂ 51	1947 May 21	6.62	3.67	2.95	1.24			98		21	Jaundice and loss of weight since Christ- mas 1946. Lapar- otomy: Ca. abd. and hepatitis.
17	H. O. ♂ 29	1942 Apr. 27	7.17	3.83	3.34	1.14	÷	÷	90	18	52	For 1 year attacks of pain with jaundice and fever. Opera- tion. Bile occlu- sion due to en- larged lymph glands.

after previous operation for cancer ventriculi. The serum proteins show some variations. In case 5 and 6 they are normal, in case 1 there is an increased A/G ratio of 3.17 due to a low globulin, in the other cases the A/G is lowered, but only in case 3 it is below 1. In this patient there was a widely spread carcinomatosis originating from a cancer coli with ulceration, stricture, edema, pleural

Table XI.
Cancer Hepatis.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
1	T. W. ♂ 63	1934 Feb. 16	6.99	5.34	1.65	3.17	÷		5		Greatly enlarged liver. Spleen palp. Ascites. Autopsy: Ca. pylori with liver metastas.
2	I. W. ♀ 41	1936 Aug. 25	6.90	3.81	3.09	1.23	÷				Cancer hepatitis with liver- and spleen enlargement. Autopsy.
3	A. G. ♂ 70	1938 Feb. 5	7.28	3.41	3.87	0.88	÷		12		Cancer coli with liver metast. Anasæra. Kachexia. Autopsy.
4	A. H. ♀ 53	June 12	7.17	3.92	3.25	1.20			6		Ca. pancreat. with liver and gland. metast. Thrombosis of vena lienalis. Varic. oesoph. Autopsy.
5	S. A. ♂ 47	1944 Feb. 10	6.90	4.38	2.52	1.74	÷	÷	4	12.1	Operation for cancer ventric. 4 years prev. Large and rugged liver. Malena.
6	J. R. ♂ 76	June 3	6.64	3.84	2.80	1.37	÷	÷	6		Op. for ca. coli 1939. Emaciation. Large and nodous liver. Lung. involv.
7	A. V. ♂ 43	1946 Mar. 9 Mar. 21	7.91 8.31	4.19 4.51	3.72 3.80	1.13 1.19	÷	÷	9	25.5	Ca. coli with liver motast. Large nodous liver. Biopsy.
8	T. M. ♂ 69	Feb. 2 Mar. 3	6.90 6.15	3.95 3.20	2.95 2.95	1.30 1.09	÷	÷	10 17	28.1 40.8	Ca. hepatitis of unknown origin. Large liver. Autopsy.
9	M. Å. ♀ 63	June 6 June 11	5.79 6.00	3.00 3.23	2.79 2.77	1.07 1.10	÷	÷	6 7	15.7	Ca. hepatitis of unknown origin. Emaciation. Edema. Ascites. Large nodous liver. Biopsy.

Table XI. (Cont.)

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Remarks
10	K. T. ♂ 62	Apr. 4 Apr. 24	6.15 5.41	3.50 2.87	2.65 2.54	1.37 1.13			10	10.2	Ca. ventriculi with wide spread involv. of liver. Ascites. Autopsy.

Table XII.

Carcinomatosis et Sarcomatosis.

No.	Name Sex, Age	Date	Total Protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Remarks
1	S. O. ♂ 65	1943 May 24 Aug. 16 Sept. 1 Sept. 28 Nov. 6	4.92 3.48 3.43 3.56 3.31	2.44 1.92 2.02 2.06 1.82	1.48 1.56 1.41 1.50 1.49	1.65 1.23 1.43 1.37 1.22	÷	÷	Carcinoma of small intestine with wide spread metastases to glands, bone marrow and liver. Edema. Ascites. Purpura. Anemia. No jaundice. Autopsy.
2	H. H. ♂ 14	1944 June 7	5.63	3.49	2.14	1.63	÷	÷	Reticulosarcoma with involv. of spleen, mediast., liver, columnna, pleurae, peritonemna. Edema. Ascites. Autopsy.
3	A. R. ♂ 27	1945 June 26	7.09	3.95	3.14	1.26			Slight jaundice (serum colour 22). Ca. ventric. with involv. of liver, kidneys, lungs, adrenals, pancreas, bones, pleurae, thyroid, Autopsy.
4	B. L. ♂ 30	July 20	6.57	4.26	2.31	1.84			General carcinomatosis with involv. of nearly all organs includ. liver. Autopsy.
5	A. S. ♀ 50	1946 Mar. 14	6.33	3.03	3.30	0.91	÷	÷	Cancer of small intestine with wide-spread metast. also in liver. Long standing diarrhea. Anemia. Acidosis. Autopsy.
6	I. S. ♀ 64	Aug. 12	5.87	3.37	2.50	1.34			Ca. ventriculi with wide-spread metast. Biopsy.
7	A. H. ♀ 64	Aug. 21	7.00	4.01	2.99	1.33			Cancer thyrcoid. with metast. Biopsy.

Table XIII.
Various Liver Diseases.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A/G	Takata	Formolgel	Serum colour	Phosphataso	Remarks
1	H. S. ♂ 49	1944 June 17	7.38	4.70	2.68	1.75				5	Polycystic liver and kidneys. No proteinuria. Urea-clear. 65 %.
2	M. K. ♀ 39	1946 Mar. 26	7.12	3.92	3.20	1.22	÷	÷		5.8	Polycystic liver and left kidney. No protein uria. Urea-cl. 60 %. Operation.
3	A. J. ♀ 61	May 27	7.16	4.20	2.96	1.42	÷	÷		6	Cystic liver and polycystic kid- neys. Trace of protein in urine. Urea cl. 64 %.
4	J. M. ♀ 49	Oct. 14 Oct. 30	6.74 6.20	3.77 3.51	2.97 2.66	1.27 1.33	÷	÷		12	Cystic liver (punc- tion.) Trace of protein in urine. Urea-cl. 63 %.
5	H. A. ♀ 39	Aug. 29 Sept. 12	6.13 6.74	3.12 3.46	3.01 3.28	1.03 1.05	÷	÷		6	Greatly enlarged liver. Several bi- opsies: Hepa- toma. Autopsy.
6	A. S. ♀ 39	1944 June 5 July 17 Nov. 13 1945 Dec. 6	7.02 6.14 7.46 7.80	4.28 3.36 4.13	2.74 2.78 3.33	1.56 1.21 1.24	÷ ÷ ÷	÷ ÷ ÷		12 6 5 6	Asthma bronchial. with chron. acet- anilid intoxica- tion. Consid. he- patosplenomeg- aly.

effusion and ascites. The lowered A/G ratios are due to low albumin in some cases and slightly raised globulin in other cases.

Carcinomatosis and Sarcomatosis.

The cases in table XII have been included to see, whether a general spreading of a malignant tumor with liver involvement, but without enlargement has any influence on the serum proteins. Only in case 3 was there a slight jaundice. It is seen that the total protein may be very low as in case 1 with values down to 3.31 % (the patient had anasarca), but with normal A/G ratios. Only in

VARIATIONS IN SERUM PROTEINS.

Table XIV. Hemolytic Jaundice.

No.	Name Sex, Age	Date	Total protein %	Albumin %	Globulin %	A G	Takata	Formolgel	Serum colour	Phosphatase	Reticulocytes %	Osmotic resistance	Remarks
1	K. H. 52	1933 Sept. 9	7.04	4.02	3.02	1.33	÷	15	13	0.40—0.54			Large spleen. Liver not palp.
2	J. F. 22	Dec. 24	7.01	4.31	2.70	1.59		26	15	0.44—0.70			Spleen palpable.
3	O. S. 71	1937 Mar. 8	6.42	4.50	1.92	2.34	÷	14	2.2	15	0.36—0.56		Spleen large. Liver palp. Died. Autopsy.
4	B. B. 57	1938 Jan. 25 Feb. 24	5.84	4.00	1.84	2.17		15	14	8	0.40—0.48 0.32—0.42		Large spleen. Liver palp. Splenectomy Feb. 2. Au- topsy.
5	O. T. 30	1943 Nov. 27	6.61	4.38	2.23	1.96	÷ ÷	30	14	0.52—0.74			Large spleen. Liver palp. Operation.
6	O. O. 51	1945 Jan. 22	6.82	3.66	3.16	1.16	÷ ÷	10	5.5	0.44—0.66			Large spleen. Liver palp.
7	M. E. 64	1944 Dec. 15	6.11	3.99	2.12	1.88	÷ ÷	30	15	0.46—0.52			Large spleen. Liver palp. Ovalocytosis.

case 5 did the ratio go below 1. This patient had a diarrhea of long standing.

Various other Liver Diseases.

Table XIII shows that the serum proteins are normal or with a slightly reduced A/G ratio in 4 cases of cystic liver, whereas in case 5, suffering from a very large liver made out by biopsy and later by autopsy to be a case of hepatoma, the A/G ratio is reduced to 1.03 due to lowered albumin and slightly raised globulin. In case 6 suffering from acetanilid poisoning (used for asthma), in which there was a considerable enlargement of liver and spleen, the A/G ratio went down from 1.56 to 0.97 during 6 months observation. The condition should probably be classified as a chronic hepatitis of toxic origin, but without jaundice.

Hemolytic Jaundice.

In 7 cases of hemolytic jaundice, some of them of the familiar, others of the acquired type, which are included in the material on account of the superficial similarity to liver cirrhosis with possible diagnostic errors, the A/G ratios are normal except in case 6, where it is down to 1.16. In one case which was splenectomized 3 weeks before, there was a slight degree of hyperproteinemia (table XIV).

Discussion.

The purpose of this paper was to examine the value of serum protein determinations in diseases in which a liver enlargement or other symptoms of liver disease constituted a diagnostic problem. Practically speaking it means the old problem of the differential diagnosis between hepatitis and obstructive jaundice due to stone or tumor, *i. e.* surgery or no surgery. It was also hoped that this kind of studies might throw some light on the question of the rôle of the liver as plasma protein producer. But this question is a rather complicated one as recent work has shown. It was already suggested by Linder, Lundsgaard and Van Slyke (1924) that the rise in globulin observed in nephrotic cases was a compensation for the loss of albumin. Björneboe (1943) looks at this compensation from the point of view of the regulation of the colloid osmotic pressure and suggests, that there is a special central mechanism for this regulation. On injecting globulin in rabbits he produced hyperglobulinemia, which was accompanied by a reduction of the serum albumin whereas injected albumin was eliminated from the blood stream or produced a lowering of the rate of albumin production (1945). He has also demonstrated that the whole increase in globulin following the injection of polyvalent pneumococcal vaccine in rabbits is identical with the antibody globulin. The wartime studies of the American workers have shown that the antibody globulin is found in the gamma globulin fraction (see Cohn). Electrophoretic fractioning of the serum proteins is therefore needed in order to determine the nature of the globulin produced in liver diseases. In hepatitis *f. i.* the globulin increase might be due both to infection and to a compensatory rise caused by a faulty production of albumin by the insufficient liver.

As to the *normal values* of the serum proteins the experience of later years indicates that these are not constant and with the increasing knowledge of their function this is not to be expected. The globulin fraction fluctuates even with minor infections like the «common cold», as pictured by the sedimentation rate. This may not affect the total protein, which is fairly constant (Lange), probably because of the behaviour of the albumin (Björneboe). The globulin content of the serum to which immunity is bound should therefore be a non constant value both in the same individual and in different persons dependant on how many and how long lasting immune bodies they carry.

Most of the external factors which can influence the serum proteins tend to lower the A/G ratio, such as infection through a rise in globulin and malnutrition by lowering of the albumin. Such facts must therefore be borne in mind, when a material like that presented here is discussed. We deal with a constantly fluctuating value like the alkali reserve, although this fluctuation usually is only moderate.

It is obvious from this material, that of the diseases in question, it is the hepatic conditions and the cirrhosis both of infectious and toxic origin, which show the most pronounced lowering of the A/G ratios. Even in acute, benign, uncomplicated hepatitis the A/G values may go down to 0.62. The material does not give any explanation why this is only found in some cases and not in others, apparently it is not only the duration, but also the intensity of the infection, which is responsible for the effect on the serumproteins. In the fatal cases of hepatitis and in the subchronic and more chronic type as well as in cirrhosis the A/G ratios always are below 1 and usually below 0.80, a ratio between 0.90 and 1 being an exception. On the other hand in obstructive jaundice due to cancer the lowering of the A/G ratio is only moderate and does not go below 0.90, except in far advanced cases beyond any surgical help. And in obstructive jaundice due to choledochus stone it is never below 1, except when cholangitic cirrhosis develops with the characteristic influence on the A/G ratio. Also the case of thrombophlebitic splenomegaly, shows clearly the effect of the developing cirrhosis on the A/G ratio.

Serum protein determinations will therefore be of considerable practical value when an existing liver enlargement with or without jaundice or a jaundice of unknown origin is up for

classification. But it must always be borne in mind, that the history and the clinical features such as findings on palpation, spleen enlargement, ascites, anemia etc. come first and the serumprotein values enter into the diagnostic considerations only at the final stage.

When the differential diagnosis between hepatitis, cancer or choledochus stone is in question a low A/G ratio below 1 speaks strongly for hepatitis and a value below 0.80 practically decides it, especially when there is a pronounced hyperproteinemia. That such a low A/G ratio also is found in cholangitic cirrhosis due to stone disease is of no consequence as the time for operation in these cases has long since been passed. On the other hand a normal or only slightly reduced A/G ratio (above 1) in a case of longstanding jaundice excludes hepatitis and speaks for cancer or stone and indicates laparotomy. The same considerations apply to a liver enlargement without jaundice. When the clinical examination leaves the diagnosis undecided, a low A/G ratio below 1 and especially if it is well below this value favours strongly the diagnosis of cirrhosis. An advanced cancer with ascites and edema may also show a low ratio (case 3, table XI), but in such a case the diagnosis is more likely to be made clinically and has no practical significance.

As mentioned above no conclusions can be drawn from the present material as to the rôle of the liver as manufacturer of the serum proteins, but the fact, that the most pronounced changes in the serumproteins are found in diseases, in which the liver is most damaged, is suggestive.

The material also permits some comparison between the *Takata reaction* and the serumproteins. Björneboe (1946) has found no relation between Takata and the serum albumin in hepatitis, but all sera with a globulin above 4 % had a positive reaction, whereas only 84 % were positive with a globulin between 3—4 %. But also some sera with a globulin below 3 % gave positive reaction. When the A/G ratio was < 1 , 98 % gave positive Takata. But Takata was also found positive in 67 % of sera with A/G ratios between 1 and 1.5.

In the present material nearly all of the cases of subchronic and chronic hepatitis (and the fatal cases) as well as cirrhosis had a positive Takata reaction and it was negative in pretty nearly all of the other diseases. But in table X are seen 2 cases of cancer with jaundice with positive Takata and one of these had a glob-

ulin of 2.80 % and an A/G ratio of 1.16. On the other hand in table III, case 11 with hepatitis had a negative Takata on two occasions with globulin percentages of 6.36 and 5.72 and A/G ratios of 0.44 and 0.42. The problem of what the Takata reaction depends on, therefore, cannot be regarded as settled, but it is a great help to know, that the reaction is positive in nearly all of the prolonged and the fatal cases of hepatitis and in 22 out of 25 cases of cirrhosis and negative in most of the surgical cases of obstructive jaundice as well as in liver enlargement due to cancer. The formolgel reaction in our material pretty nearly follows the Takata reaction.

As to the *phosphatase* values they vary so much, that we do not pay much attention to them in our diagnostic considerations.

It has been the tendency lately to explain the ascites occurring in hepatitis and cirrhosis as caused by the low colloid osmotic pressure of the serum as a consequence of the changes in the serum proteins (Björneboe 1946). Björneboe found the formula $2.52 \text{ alb.} + \text{glob.} = 13.1$ for the serumproteins in cases without ascites and below this value, if this symptom was present. If we apply this formula to our normal values for the serum proteins in table I, we obtain values between 12 and 15.4 (average 13.9). If we apply it to the figures of tables II, III and IV, mostly all of the values fall below 12, both in ascitic and non-ascitic cases, except in some instances of hyperproteinemia, when they may reach 15 and 16 and in case 11 of table II *with ascites*, where it was 13.4, whereas other patients may have a value as low as 7.16 without ascites. Low osmotic pressure may therefore be a contributing factor, but not the dominating one as also the experiments of Thorn et. al. (1946) on the effect of saltpoor concentrated human serum albumin in ascitic cases tend to show. Only when the ascites was part of a general anasarca did they obtain diuresis following this treatment, not when there was ascites alone.

Summary.

The purpose of this paper was to examine the diagnostic value of serum protein determination in liver diseases by the Howe method (with a slight modification to obtain more rapid and thorough digestion).

In 14 normal men and 6 normal women the total protein varied between 6.11 and 7.62 (average 6.96), the albumin between

3.90 and 4.97 % (average 4.59), the globulin between 1.69 and 2.93 % (average 2.37) and the A/G ratios between 1.49 and 2.85 (average 1.97).

In 148 cases of various liver diseases chosen with the point of view of differential diagnosis the following results were found:

In *acute benign hepatitis* (24 cases) the A/G ratios varied between 0.57 and 1.71; of 34 determinations 18 were below and 16 above 1. There was distinct hyperproteinemia in 4 cases.

In *hepatitis* ending fatally or turning chronic (25 cases) the A/G ratios were always below 1 except in 2 cases during temporary improvement, when they rose to 1.16 and 1.07 respectively. Of 78 determinations 68 showed an A/G ratio below 0.80 with a lowest value of 0.12. In 10 of the 25 cases was observed an often considerable hyperproteinemia with a maximum of 12.29 %, due to an often enormous rise in the globulin (up to 10.30 %). All of them had hypoalbuminemia.

In *toxic hepatitis* due to medication (5 cases) the A/G ratios were normal in 3 and below 1 in 2 of the cases, of which the last one was a case of acute yellow atrophy with an A/G of 0.59.

In *cirrhosis* (26 cases) the A/G ratios were all below 1; of 48 observations only 2 had A/G ratios between 0.90 and 1 and 38 had ratios below 0.80 with a minimum of 0.07. All of them had hypoalbuminemia.

In a case of *thrombophlebitic splenomegaly* the A/G ratio fell to 0.74 during a 10 years observation as cirrhosis developed.

In *gallstone occlusion with icterus* (11 cases) the A/G ratios were always above 1, except when cholangitic cirrhosis developed, when it was found below 1.

In *gallstone without icterus* (9 cases) the A/G ratios were normal or nearly so.

In *obstructive jaundice due to cancer* or glandular tumor (17 cases) the A/G ratios were always lowered and varied a little on both sides of 1, but never below 0.90, except in a far advanced case with ascites and edema, where it was 0.83. Of 28 determinations 11 lay between 0.90 and 1 and 17 above 1.

In *cancer hepatitis* without jaundice (10 cases) all of the A/G ratios were above 1 except in a kachectic case with anasarca, where it was 0.80.

In *carcinomatosis and sarcomatosis* (7 cases) the A/G was 0.91 in one out of 11 determinations, all the others were slightly reduced, but above 1.

In 6 cases of *liver enlargement* of various causes the A/G ratios were normal or somewhat reduced, but all of them above 1, except in a case of acetanilid poisoning with hepato-splenomegaly, where it was 0.97.

In 7 cases of *hemolytic jaundice* the A/G ratios were all very high except in one case, where it was 1.16.

The *Takata reaction*, which was positive in nearly all of the cases of fatal or chronic hepatitis and cirrhosis, was not invariably related to the A/G ratio or the globulin content.

The *phosphatase reaction* varied so much, that it was no help to the diagnosis.

The relation of ascites to the serum protein changes are discussed.

Conclusions.

Because of the behaviour of the serumproteins in liver diseases as summarised above, their determination may be of the greatest help to the diagnostician, but only after the most careful history and clinical examination. It is especially in jaundice of longer duration, when the question of surgery or no surgery has to be decided and of liver enlargement without jaundice, that an A/G below 0.90 and especially lower than 0.80 practically decides the diagnosis of hepatitis or cirrhosis, if the clinical examination also fits in. It may also be a help to know, that a pronounced hyperproteinemia due to globulin increase has not been observed in this material outside hepatitis and cirrhosis.

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On the Effect of Some Common Gastric Drugs on the Motility of the Stomach.

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As previously reported by Brummer and Wegelius, motility disturbances of the stomach can be established by X-ray with the majority of persons suffering from gastric distress, whereas most healthy persons are not found to have such disturbances. Accordingly a definitely more distinct relation can be indicated between gastric distress and motility disturbances than between gastric distress and chronic gastritis, not to speak of secretory disturbances. Brummer and Wegelius therefore assume motility disturbances of the stomach to be the probable direct cause of gastric distress; the diagnosis would thus be gastric dystonia and not dyspepsia. The type of motility disturbance is evidently of less significance in this connection than the tendency to such disturbances, for, as already indicated by Weltz and as clearly revealed by the investigations described in the present paper, the type of motility disturbance established may vary from time to time. For instance, one examination may disclose with the same patient a greatly increased peristalsis and another examination a total absence of peristalsis.

It is the object of the following paper to endeavour to find additional corroboration for the hypothesis presented on the significance of motility disturbances as cause of gastric distress by describing X-ray observations of the effect of various gastric drugs on the motility of the stomach, for in case motility disturbances truly are the cause of gastric distress it can be expected that drugs

which give relief to the symptoms of distress will be found to affect gastric motility when the question is not of a purely narcotic effect. It is not proposed to deal in the present connection with the effect of different drugs on gastric motility in the full extent of the question but merely to endeavour to study the effect in this respect of a few of the most common gastric drugs when administered per os in the usual therapeutic doses.

Of the drugs investigated, the action of atropine and papaverine has already in the past been considered to be due to their antispasmodic effect, in other words to direct action on gastric motility. On the other hand, the relief obtained in gastric distress from various antacids is generally ascribed to their power to neutralize hydrochloric acid. Hydrochloric acid, again, has been regarded as a substitute for absence of gastric acid regardless of the fact that even a dose of 4 ml diluted hydrochloric acid taken with meals has no effect worth mentioning on gastric acidity (Brummer).

The drugs under observation in the present study in regard to their effect on gastric motility are atropine, sodium barbital as representative of the barbiturates, papaverine, hydrochloric acid, and various antacids. The method followed in the observation of the first three drugs comprised a number of X-ray examinations on separate days. Before one of these examinations — the control examination — no drug was administered; one half to one hour before all the other examinations the patient received a dose of the drug then under observation. A different order of examination was followed for each patient, and the X-ray investigator (Bundul) had no knowledge of the drug used in the specific case being examined. With the doses of hydrochloric acid and antacids, the usual X-ray examination was first performed, followed by administration of the drug and observation of possible resultant variations in gastric motility. Attention was paid to peristalsis and tone of the stomach and the duodenum and to any deviations from the normal in them. As was already mentioned, considerable variation in the type of motility disturbance could often be observed in the same patient at the different examinations, and for this reason importance cannot be given to the results of individual examinations but only to the combined result of several examinations. The drugs observed were, as stated, administered per os.

All the patients observed were hospitalized for treatment in the medical department of the Provincial Hospital at Oulu. The material consists mainly of patients complaining of the usual,

so-called dyspeptic distress; however, in view of what has been stated earlier in this paper, the term dyspepsia will be herein substituted by the diagnosis gastric dystonia. Some cases of peptic ulcer and gastric carcinoma and a few healthy persons are also contained in the material. A total of 137 persons were studied, with 316 X-ray examinations performed. A closer description of the material in each instance is obtained from the account on the results obtained with the several drugs. In addition to the X-ray examination, the usual gastric analysis was carried out in the case of a part of the patients in the manner more fully described in an earlier paper by Brummer on gastric motility disturbances.

Atropine.

It is generally regarded that atropine has an inhibitory effect on the motility of the stomach by reducing both peristalsis and tone. Its effect lies mainly in a paralyzing action on the vagus; Barsony and v. Friedrich have found it to also directly affect the stomach muscles. In animal experiments in particular, the inhibitory action of atropine on peristalsis and tone is clearly evident when the drug is administered in sufficiently large doses (*c. g.* Zuntz and Tyrebaert, Smith). According to Lockwood and Chamberlin, on the other hand, the human stomach is considerably less sensitive to atropine than that of animals, and for this reason they hold that only the maximum doses are sufficient to shorten the emptying time. Inhibition of gastric motility in man with doses ranging from 0.5 to 1.5 mg is established by i. a. Östvös, Lasch, Petrovic and Tetelbaum. Östvös also finds that atropine in doses of 0.5 to 1.0 mg may, in addition to inhibitory effect, also cause pylorospasm, as had already been indicated by Wertheimer and Boulet with large doses. A relatively negative attitude toward peroral atropine therapy is taken by Bastedo, who is of the opinion that the doses required to produce an effect on gastric spasms are so large as to produce unpleasant by-effects.

In our own material the effect of atropine was observed with 40 patients. Thirty-three complained of gastric dystonia distress, a peptic ulcer was established with two and a gastric carcinoma with 3 patients, one had a disease of the bile duct, and no gastric symptoms were established with two.

The dose was 0.5 mg atropine sulphate, administered per os one-half to one hour before X-ray examination.

In the control material peristalsis was normal with 11 patients and tone with 25; increased peristalsis was found with 12 and increased tone with 5 patients; with 17 and 10 patients respectively they were decreased.

Following the administration of the atropine, peristalsis was normal with 5 and tone with 20 patients, both peristalsis and tone were increased with 8, and peristalsis was decreased with 27 and tone with 12 patients. These results already indicate that the dose of atropine administered apparently decreases the peristalsis to some extent, whereas no effect can be observed in regard to the tone. The effect on the peristalsis can be seen still more clearly by observing the change after atropine in each individual case as compared with the control examination. It was then found that the peristalsis was unchanged with 9, increased with 7, and decreased with 24 patients. For tone the corresponding figures were 16, 11 and 13.

On the basis of these results it can be stated, corroborating earlier finds reported in the literature, that a dose of 0.5 mg of atropine administered per os apparently has a decreasing action on gastric peristalsis; on the other hand, no effect on the tone could be established. The decreasing action of atropine on the peristalsis is not, however, so strong — at least not at the doses used in these cases — as to bring out the action in every instance. In those cases where peristalsis appeared to have increased after atropine, this probably is not accountable to the drug, a more natural explanation probably being that in these cases atropine was not able to inhibit spontaneous variations in a pathologically sensitive gastric peristalsis.

Sodium Barbital.

We have found in literature no detailed information on the effect of barbiturates on gastric motility.

The investigations were carried out with the same material as those on atropine, and each patient was accordingly subjected to X-ray examination three times. After inclusion of one person with no gastric symptoms the material totalled 41 cases.

Prior to the X-ray examination 0.1 g of sodium barbital was given to the patient. The examination disclosed that the peristalsis, in comparison with the findings in the control examination,

was unchanged with 10, increased with 22, and decreased with 9 patients. For the tone the figures were 18, 12 and 11 respectively.

As was the case also with atropine, no effect on the tone could be established with the administered dose of sodium barbital, but there apparently was a slight increase in the peristalsis. This effect, which at first may seem somewhat surprising, is apparently due to barbiturates having — like all thalamic narcotics in general — a stronger sympathetic than parasympathetic inhibitory effect, the result being a relative increase in the vagus tone, in a similar manner as in physiologic sleep. As is known, barbiturate poisonings bring on increased gastro-intestinal motility, such as a tendency to vomiting and diarrhea.

Papaverine.

Gross and Slaughter have found with animal experimentation that 2 to 6 mg of papaverine per kilogramme administered intravenously or intramuscularly reduces the peristalsis and tone in the stomach but not in the small intestine. The same observation was made already earlier by i. a. Plant and Miller. On the other hand, Barsony and v. Friedrich were unable to find any effect on the human gastric tone and peristalsis or on the opening and closing of the pylorus with intravenous doses of 0.01—0.08 g or intramuscular doses of 0.12 g. Information on the action of papaverine on pylorospasms is somewhat contradictory. According to some investigators papaverine can always or nearly always reduce these spasms, whereas other investigators consider its effect uncertain in most cases (Holzknecht and Sgalitzer, Szerb and Révész, Schlesinger, Erdélyi).

In the present material the effect of papaverine was observed with 36 patients, of which 29 belonged to the gastric dystonia group, 3 complained of no gastric distress, 2 were patients with peptic ulcer, and 2 with gastric carcinoma.

A dose of 0.05 g of papaverine hydrochloride was given per os to 25 of these patients prior to the X-ray examination. A comparison with the control examination disclosed that the peristalsis was unchanged with 6, increased with 10, and decreased with 9 patients. For the tone the figures were 18, 3 and 4 respectively. According to these results the administered dose of 0.05 g had no effect on the gastric peristalsis and tone, nor could any change be observed in the duodenal motility.

In view of this negative find the remaining 11 cases were given a larger dose of papaverine, consisting of 0.1 g administered likewise per os one-half to one hour before the X-ray examination. In several of these patients lassitude was clearly observable after taking the drug.

Even with this dose no effect on the gastric peristalsis and tone could be established. For instance the peristalsis was unchanged with 3, increased with 4, and decreased also with 4 patients. However, an effect was found on the duodenal motility. The peristalsis and tone of particularly the bulbus duodeni decreased distinctly. The bulbus either filled poorly or filled atonically, whereafter the contrast medium ceased to move; when the bulbus was pressed to empty it, the contents generally passed back into the stomach. Changes of this kind in the motility of the duodenum were established with 10 patients out of the 11 examined; with 2 patients also duodenal retroperistalsis was observed.

Corroborating the statements made in the literature, the present investigations disclose no effect on gastric motility with the administered doses of papaverine, but the dose of 0.1 g apparently had action on the duodenal motility.

Hydrochloric Acid.

In 1907 Cannon presented his well known theory on acid control of the pylorus, according to which increased gastric acidity causes the opening and increased duodenal acidity the closure of the pylorus. This opinion, on the basis of which the theory of rapid emptying of an achlorhydric stomach was developed, has in the light of modern research proved erroneous, for there is no separate contraction of the pylorus, it being a part of the peristalsis of the stomach. According to several investigators (*e. g.* McClure et al., Baird et al., McCann) the acidity of the contents of the stomach and duodenum has no effect on the emptying time of the stomach. Brummer, using methylene blue as indicator, could also establish no difference in the emptying time whether the achlorhydria patient took water or hydrochloric acid on an empty stomach.

In the present investigations the effect of hydrochloric acid on gastric and duodenal motility was observed with 13 patients, with 4 of whom insulin-proved achlorhydria was established; among the latter were 2 patients suffering from addisonian per-

nicious anaemia. The usual gastric X-ray examination was first performed, after which the patients received 1 ml of diluted hydrochloric acid in 1 dl of water.

Changes in the gastric tone were not established with patients. With 5 patients, one of whom suffered from achlorhydria, no effect could be found even on the gastric peristalsis; with 4 patients, two of whom had achlorhydria, the peristalsis was slightly decreased after administration of the drug but in one of these it again increased after 10 minutes; with the remaining 4 patients, 1 of whom suffered from achlorhydria, a very slight increase of the peristalsis was found. To summarize it therefore can be stated it could not be established that the administered dose of hydrochloric acid has any distinct effect on the gastric motility.

The duodenal motility and in particular its retroperistalsis was found to increase during the examination of 6 cases. After administration of the hydrochloric acid the contrast medium at first moved backward and forward in the duodenum, returning partly to the stomach, and only after some time was able to pass onward to the intestine. It may be mentioned that retroperistalsis which was as clearly distinguishable could be established in the entire material only once in the control examination. Two of the 6 patients with whom hydrochloric acid was found to act on the duodenal peristalsis suffered from achlorhydria.

Summarizing these results it can be stated that the administered dose of 1 ml of diluted hydrochloric acid has no distinct effect on gastric motility, but in a part of the cases it caused increased peristalsis and particularly retroperistalsis of the duodenum, which seemed to be independent of whether the patient had acid gastric secretion or not.

Antacids.

Investigations were performed with the following antacids: Sodium bicarbonate, calcium carbonate, magnesium carbonate, magnesium oxide and »Ventrakon» prepared by Orion Pharmaceutical Factory and containing per 100 g: 12 g aluminium hydroxide, 5 g calcium phosphate, 23 g magnesium peroxide (25 %) and 60 g bolus alba. In accordance with information previously given in the literature it is generally claimed that sodium bicarbonate increases and magnesium compounds decrease the gastric motility (Meyer and Gottlieb: Die exp. Pharmakologie).

In the investigations the following doses were administered to the patients: ca. 7 g sodium bicarbonate, ca. 5 g calcium carbonate, ca. 2 g magnesium oxide, and ca. 6 g Ventracon. With the exception of Ventracon the neutralizing property of these amounts is approximately equivalent, ranging from 70 to 90 ml of 1 N HCl, whereas 6 g Ventracon can only neutralize from 35 to 40 ml of 1 N HCl. That Ventracon was administered in doses only half as large as the others with respect to its neutralizing property was due to the fact that an unsuitably large volume would have been required to achieve with it the same neutralizing effect as with the other substances.

The results obtained were as follows:

1) Sodium Bicarbonate.

The material consisted of 10 patients with gastric dystonia. Four of them were found to have insulin-proved achlorhydria; 2 of the latter suffered from Addisonian pernicious anaemia. Further there were 2 patients with peptic ulcer and one with gastric carcinoma.

The peristalsis was observed to increase after the administration of sodium bicarbonate in all of the 10 patients first mentioned. The increase was very distinct with 9 patients and less pronounced with one. As a rule ten minutes subsequent to the patients' receiving the dose a deep and large wave of peristalsis was visible moving through the stomach. In two of the cases also the tone seemed to increase. The effect of the sodium bicarbonate was as distinct with the patients with achlorhydria as with the others. No definite effect was observed with one of the peptic ulcer patients and the carcinoma patient.

2) Calcium Carbonate.

Six patients with gastric dystonia and one with peptic ulcer were examined. Two of the former were found to have insulin-proved achlorhydria.

The calcium carbonate had no effect on the gastric peristalsis or tone of 3 of the patients among whom were both the achlorhydria cases. With 4 patients a slight increase of peristalsis was observed. Thus calcium carbonate possibly has a slightly increasing effect on gastric peristalsis, which is not however manifested by an achlorhydric stomach evidently due to the insolubility of the calcium carbonate.

3) Magnesium Carbonate.

The effect of magnesium carbonate was observed with 14 patients. Peptic ulcer was established with 2 of them, while the remaining 12 belonged to the gastric dystonia group. Insulin-improved achlorhydria was present in 3 of the latter.

Gastric peristalsis increased subsequent to administration of the magnesium carbonate distinctly with 3 patients and less distinctly with 8 of them, whereas no effect could be observed with 3, among whom were 2 patients with achlorhydria. With respect to tone no effect was observed. Very typical of magnesium carbonate was its effect on the duodenal peristalsis, which increased with 8 patients, with 7 of whom distinct retroperistalsis was also manifested. Taking into consideration the effect of this drug both on the gastric and the duodenal peristalsis, the material includes only 2 cases where no effect was established. Since both of these were patients with achlorhydria it appears that the effect of this drug, which is not easily soluble, is dependent on the presence of hydrochloric acid, which also was the case with calcium carbonate.

4) Magnesium Oxide.

The material comprised 3 patients with peptic ulcer, 2 with no gastric symptoms, and 11 with gastric dystonia. Insulin-improved achlorhydria was present with 3 patients.

This drug was not found to have any effect on the gastric motility with 4 of the patients, 2 of whom had achlorhydria, whereas it was observed that the gastric peristalsis increased slightly with 10 and distinctly with 3 patients. No effect on the gastric tone was established. Like magnesium carbonate, magnesium oxide also increased the duodenal peristalsis. With 9 of the 17 patients examined it was observed that the duodenal peristalsis increased after administration of magnesium oxide; retroperistalsis was in evidence with only one patient. No effect was noted with 2 of the achlorhydria patients and even with the third the increase of gastric peristalsis was hardly evident.

The effects of magnesium oxide and magnesium carbonate resemble each other in many respects, the former, however, being evidently somewhat slighter than the latter. The effect of magnesium oxide on patients with achlorhydria, like that of other antacids not easily soluble, was less evident than on patients with acid gastric secretion. The effect of the magnesium salts on

duodenal peristalsis must doubtless be collocated with their promoting effect on bile secretion.

5) Ventracon.

Twelve patients were examined. Two of them had no gastric symptoms, and the rest suffered from gastric dystonia. Achlorhydria was established with 4 of them.

A distinct increase of gastric peristalsis was observed with only one of the achlorhydria patients. No effect was perceived with 2, one of whom had achlorhydria. With the remaining 9 patients gastric peristalsis increased only slightly after administration of Ventracon. An effect on the duodenal peristalsis was seen only with 2 patients. Thus the effect of Ventracon on gastric and duodenal peristalsis seems with most patients to be slight and evidently independent of gastric acidity.

Discussion.

In summarizing the observations presented above it may be stated that most of the drugs under observation have, when administered in the usual therapeutic doses, a more or less distinct effect either on gastric or duodenal motility or on both. Atropine decreases gastric peristalsis, whereas sodium barbital increases it. Sodium bicarbonate has a distinctly increasing effect on gastric peristalsis, which is also true of the other antacids employed, though the effect is considerably slighter. The magnesium salts have also an effect on the motility of the duodenum. Likewise hydrochloric acid had an effect on the motility of the duodenum, but no distinct effect on the motility of the stomach was to be observed. Only papaverine in a 0.05 g dose failed to have any effect perceivable, but when the dose was increased to 0.1 g it decreased the motility of the duodenum and particularly that of the bulbus duodeni, whereas it had no observable effect on the stomach.

The fact that the drugs which relieve gastric distress generally have an effect on gastric or duodenal motility gives rise to the idea that their therapeutic effect may at least partly be due to the latter effect. In the following this question is dealt with in detail with reference to the several drugs in the light of the results presented above and of some additional experiments.

It is already earlier generally regarded that the effect of atro-

pine on gastric distress is based at least partly on its antispasmodic property. Tetelbaum and others have stated that, at the same time as the gastric peristalsis is inhibited by atropine, the patient's distress is relieved. The inhibitory effect of atropine on gastric peristalsis was also observed in the authors' investigations. Furthermore it has been claimed that atropine prevents gastric secretion and consequently relieves hypothetic distress caused by hypersecretion. However, the authors have found with gastric patients, some of whom had achlorhydria and some acid gastric secretion, that atropine relieves gastric distress with equal success in both groups, wherefore it is evident that its therapeutic effect may not be based on its inhibitory action on gastric secretion.

The use of hypnotics, particularly the barbiturates, in gastric distress, especially nausea, has been accounted for because of their sedative effect on the stomach. The opinion may also be held that particularly in nausea, where the stomach is frequently roentgenologically entirely atonic at least at the initial phase, the peristalsis-increasing effect of the barbiturates, which was established above, promotes evacuation and consequently relieves distress.

The effect of papaverine has also previously been considered to be due to its antispasmodic properties. It is not known to have any effect on secretion. But, since the 0.05 g dose, which according to tests made by authors also relieves gastric distress in many cases, has no effect on the motility of the stomach, as it was established above, it seems more natural to conclude that its effect is for the great part purely narcotic.

Hydrochloric acid has been one of the most popular and uncritically used gastric drugs for the last fifty years. It has been believed for instance to promote peptic digestion and consequently relieve gastric distress. As Brummer has demonstrated, the therapeutic results claimed to have been obtained by it have at least in part been of a psychotherapeutical nature. For, as it has already been mentioned in an earlier paper, even 4 ml of diluted hydrochloric acid taken during a meal has no noteworthy effect on the acidity of the gastric contents and consequently has no promoting effect on peptic digestion. This dose can only make the contents of an empty stomach slightly acid for some time. Admittedly, there are cases in which hydrochloric acid has a favorable effect on gastric distress without any psychotherapeutic factors. Thus, in the therapeutic experiments with antacids

described below it was found with a female patient that neither sodium bicarbonate nor magnesium oxide relieved her gastric distress, whereas hydrochloric acid did. The patient had never used the latter before, wherefore she was not familiar with its taste. It was roentgenologically verified that hydrochloric acid had a distinct effect on her duodenal peristalsis, and all gastric analyses revealed normal acidity. It appears that the relieving effect of hydrochloric acid — when it is actually verified — can more easily be accounted for on the grounds of its effect on motility than for instance of a promoting effect on chemical digestion particularly when, as in the above case, the therapeutic as well as the motility effects of hydrochloric acid are not necessarily connected with gastric acidity.

The general conception is that the effect of the antacids is due to their neutralizing property. Furthermore, it is mentioned in the literature that in using antacids containing carbonates, carbonic acid is released in the stomach through the effect of hydrochloric acid and it is supposed to have sedative effect on the stomach. In this connection attention has not been drawn to the peristalsis-increasing effect of sodium bicarbonate, which has been known for a long time.

If the relieving effect of antacids on gastric distress were based on their neutralizing property, first, the latter should be dependent on gastric acidity, and, second, one would expect the therapeutic effect of the several antacids to be at least in some proportion to their neutralizing property. The first condition does not hold good, for as among others Brummer has stated, sodium bicarbonate more frequently gives relief in the gastric distress of patients with achlorhydria than hydrochloric acid. With the purpose of going into this question more thoroughly and comparing the relief to gastric distress given by different antacids, therapeutic experiments were performed with natrium bicarbonate, Ventrakon and magnesium oxide. Patients were told that they will be given two drugs and were requested to state which of them gave greater relief to their gastric distress. The doses administered were: 1 g sodium bicarbonate and 2 g Ventrakon (the neutralizing property of each is from 10 to 15 ml 1 N HCl) and 1 g magnesium oxide, the neutralizing property of which is greater than that of the first mentioned drugs (ca. 35 ml 1 N HCl).

A comparison was made between the therapeutic effects of sodium bicarbonate and Ventrakon with 38 patients, 3 of whom

suffered from peptic ulcer and the remaining 35 from gastric dystonia. Insulin-proved achlorhydria was present with 12 of the latter group. Twenty-one of the patients considered sodium bicarbonate more relieving and 10 Ventracon. Of the first group 8 had achlorhydria and of the second 4. Of the 7 remaining patients 4 felt equally relieved by both the drugs, and 3 felt that neither one have any relief.

A comparison was also made between the therapeutic effects of sodium bicarbonate and magnesium oxide on 21 patients with gastric dystonia; 6 of them were found to have achlorhydria. Eighteen, among them all the achlorhydria patients, preferred sodium bicarbonate. The remaining 3 considered both equally good.

The results confirm the observation that the relieving effect of sodium bicarbonate on gastric distress is independent of the gastric acidity. Also Ventracon seems to relieve the distress of achlorhydria patients. As it was stated above, the effect of both the drugs on also the motility of the stomach was independent of gastric acidity. Further, the experiments show that sodium bicarbonate, which has roentgenologically the most distinct effect on the motility of the stomach, is also considered by most of the patients to give the best relief in their gastric distress, regardless of the fact that the neutralizing property of the dose of Ventracon was equal to and that of the dose of magnesium oxide from two to three times as great as that of the sodium bicarbonate dose.

The authors draw the conclusion from the experiments that it is more probable that the relieving effect on gastric distress of the different antacids is due to their effect on the gastric motility than to their neutralizing property.

To summarize, the observation may be made that the drugs experimented generally affect the gastric motility more or less distinctly even when administered in only the usual therapeutic doses, and that it is highly probable that their relieving effect on gastric distress is at least partly due to the said effect on motility, which confirms the hypothesis presented in the beginning with reference to the significance of motility disturbance in the etiology of gastric distress.

The hypothesis that an explanation for the effect of gastric drugs is at least partly to be found in their effect on the motility of the stomach opens new vistas to attaining causal medical therapy in gastric distress. Perhaps by following this conception we

can in the future find a better explanation than hitherto for the therapeutical results that at present seem so arbitrary — that is, find an answer to why sodium bicarbonate has a better effect on one patient and Ventracon on another, and perhaps hydrochloric acid on a third one, and why atropine is more suitable for one patient and papaverine for another, etc. Meanwhile we can only ascertain that the evident cause, at least for a considerable part, of gastric distress is disturbances in the motility of the stomach, wherefore different drugs, each of which affects the gastric motility in its own typical way, give relief. That the suitability of a drug varies with different cases depends upon factors as yet unknown, such as perhaps the type and degree of the disturbance in motility, the reactions of the organism of different individuals, etc. However, it seems possible that by continuing experiments on the above explained foundation we shall with greater probability be able to find the laws governing the said therapeutic effect than in the light of, for instance, disturbances in gastric secretion.

Summary.

The authors have performed X-ray examinations on the effect of the usual gastric drugs on the motility of the stomach. The drugs used were atropine, sodium barbital, papaverine, hydrochloric acid, and five different antacids, viz. sodium bicarbonate, calcium carbonate, magnesium carbonate, magnesium oxide, and »Ventracon» (Orion's preparate containing per 100 grammes, according to manufacturer's statement, 12.0 g aluminum hydroxide, 5.0 g calcium phosphate, 23.0 g magnesium peroxide (25 per cent) and 60 g bolus alba). The drugs were administered per os, generally in the usual therapeutic doses. 137 patients underwent observation, and the number of X-ray examinations totalled 316.

It was established that atropine decreased and sodium barbital increased the gastric peristalsis. After a dose of 0.05 g of papaverine no change could be observed, whereas 0.1 g of papaverine had a decreasing effect on the peristalsis and the tone of the duodenum and of the bulbus duodeni in particular; on the gastric motility even this dose was found to have no effect. Hydrochloric acid, likewise, had no distinct effect on the gastric motility, while it increased the duodenal peristalsis, causing in particular retroperi-

stalsis. Among the antacids, sodium bicarbonate very clearly increased the gastric peristalsis, which was also true, although in a less marked degree, of the other antacids used; the magnesium salts furthermore acted on the duodenal peristalsis.

It is the opinion of the authors that the benefit derived by patients from the drugs under observation is due to their effect on gastric and duodenal motility. This opinion was confirmed by certain comparative therapeutic experiments carried out with antacids, in which it was established that sodium bicarbonate, which had the most distinct effect on the gastric motility, relieved the gastric distress of the patients distinctly better than magnesium oxide or Ventracon, regardless of the fact that the neutralizing properties of the administered Ventracon dose were as great, and those of the magnesium oxide dose two or three times as great as those of the sodium bicarbonate. Also it appeared that the therapeutic effect of sodium bicarbonate and Ventracon as also the effect of these antacids on the gastric motility was independent of the patient having achlorhydria or an acid gastric secretion.

The authors state in conclusion that although it accordingly appears probable that the relief obtained in gastric distress from various drugs is due at least in part to their effect on gastric motility, the details of this effect are still unsolved and it therefore is not known why one patient obtains more relief from sodium bicarbonate and another patient e. g. from Ventracon, while others may find atropine, papaverine or some other drug more suitable. It merely is evident that the motility disturbances which underlie gastric distress are in one case affected more beneficially by a different drug than in another case. However, it is possible that continued research based on the finds described above may shed more light on the question and increase our knowledge of the causal therapy of gastric distress.

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The Hypertensive Diencephalic Syndrome (Page).

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Page¹ describes a »hypertensive diencephalic syndrome» which he observed especially in young or middle-aged women. It is characterized by labile hypertension and by the periodical appearance of red patches on the skin of the neck and chest. The extremities are cold and pale. In some cases there are fits of weeping even when no emotional cause is present. As a rule tachycardia and accentuated peristalsis are observed. These phenomena become particularly marked under the influence of excitement, but may also occur without any obvious cause.

A diagnosis of thyrotoxicosis is frequently made on the basis of these symptoms, the more so as the thyroid gland is usually slightly enlarged and the basal metabolic rate often raised (+10—+30 %). Subtotal thyroidectomy gives no result »yet it is the rare patient who escapes the operation». Page used the term »diencephalic syndrome» because the signs can be provoked by diffuse stimulation of the diencephalon in human beings.

We have had the opportunity of examining a number of patients with this syndrome; some case-histories are following:

Case 1. A woman aged 61 years complained of being quickly tired. She was very nervous and was no longer able to cope with her housework. She sweated a great deal, could stand cold weather better than hot, but often suffered from cold feet. She was very liable to tremors and often suffered from palpitations. Recently she had lost some weight. For some years she had been suffering from diabetes mellitus.

¹ Page: Am. J. Med. Sciences, 190 (1935) p. 9. Page & Corcoran: Arterial Hypertension, 1946.

The patient's manner was anxious and flurried. She was fairly well-nourished: height 1.53 m, weight 58 kg. After she was undressed there appeared on the neck and chest red patches which lost their colour on pressure. The pulse was 144, blood-pressure 210/105. The thyroid gland was just palpable and not enlarged. The heart was enlarged to a finger's breadth beyond the medioclavicular line; at the apex a systolic murmur could be heard and the aortal second sound was accentuated. The liver could be felt for a breadth of two fingers under the costal arch. A fine tremor was present in both hands. The urine contained 5 % glucose and no acetone. The blood sugar was 211 mg %. The basal metabolism was +62 %. Blood cholesterol 1.88 %₁₀₀. The renal function was good.

Case 2. A 49 year old woman had suffered for 12 years from high blood pressure; this had been noticed at the time of the birth of her youngest child. She had been putting on weight since her 27th year. From girlhood she had been troubled with migraine. For the past few years she had been seized now and then by severe pain in the upper part of the left leg, later also in the lower part of the leg. This pain often occurred at night and not specially upon walking. She tended to sweat freely and had never been a «shilly» person, but complained frequently of cold feet. In the last few years she had sometimes had attacks of shortness of breath at night, with considerable coughing. Any extra exertion also brought on shortness of breath. The appetite was unimpaired; defaecation and micturition normal.

The patient was strongly built and well nourished (height 1.70 m, weight 83.8 kg). After she was undressed numerous red patches appeared on the neck and chest. Blood pressure 215/105, pulse regular and full, 88 per min. Thyroid not enlarged. Eyes normal. The heart was enlarged to the left; the beat was palpable at a breadth of two fingers beyond the medioclavicular line. Over the apex and the aorta a systolic murmur was audible with accentuated aortal second sound. Over the lower posterior part of the left lung numerous moist fine vesicular rales were heard. The liver was palpable to a breadth of 4 fingers under the costal arch. In the upper part of the left leg the oscillations were smaller (2—1) than in the upper part of the right leg (3—2).

The basal metabolism was +38 %. Blood cholesterol 2.4 %₁₀₀. Sedimentation rate 22 mm after one hour; leukocytes 7,200; eosinophiles 1 %; staff cells 2 %; segmented cells 69.5 %; lymphocytes 25 %; monocytes 2.5 %. The renal function was good. The electrocardiogram showed a left type with negative T².

Case 3. A woman of 56 had been in a very nervous and anxious condition for some years. She sweated considerably but suffered from cold feet. She could stand cold better than heat. She had not lost much weight, suffered occasionally from tremors and also from palpitations.

The patient was well built and fairly well nourished (height 1.66 m, weight 53.5 kg). She also showed the typical red patches on neck and chest. Pulse regular and equal, rate 104; blood pressure 205/130.

The thyroid gland was enlarged and had a few nodules.

The heart was enlarged to the left to a finger's breadth beyond the medioclavicular line. Lungs, liver and spleen were normal. The basal metabolism was +45 %. Blood cholesterol 2.61 ‰. Sedimentation rate, 13 mm. after one hour. Leukocytes 11,000; eosinophiles 0.5 %; staff cells 2.5 %; segmented cells 63.5 %; lymphocytes 27.5 %; monocytes 6 %. The renal function was good. Intravenous pyclograms showed no abnormalities.

The electrocardiogram was normal.

Case 4. A woman aged 55 sought treatment for nausea, tremulousness, excessive sweating and liability to fatigue. She suffered a great deal from cold feet. The blood pressure was 230/130, pulse approx. 96 per min. The thyroid gland was enlarged equally in all directions.

After undressing there were red patches on neck and chest. The heart was enlarged to the left (ictus cordis one finger's breadth beyond the medioclavicular line). Over the apex and the aorta a systolic murmur was heard which was conducted over the great vessels. The aortal second sound was accentuated. There were no signs of congestion. The kidneys concentrated adequately; the urea content of the blood was normal. Nothing abnormal was found in the urine. The basal metabolism was raised: +39 %. The cholesterol level of the blood was increased: 3 ‰.

Case 5. A woman of 59 complained of pain in the heart, liability to fatigue and palpitations. She was very nervous, did not sweat much but was rather «chilly». The typical flushing of the neck and chest was noted. Blood pressure 235/150, pulse 124. Thyroid not enlarged. The heart was enlarged to the left; systolic murmur over the apex and aorta with accentuated aortal second sound. The basal metabolism was +31 %. Blood cholesterol 2.81 ‰.

Case 6. A woman of 61 with palpitations, cold feet and hands and the typical symptoms of diabetes mellitus. She also showed the typical flushing; pulse 80; blood pressure 235/130; basal metabolism +54 %; blood cholesterol 2.96 ‰. The thyroid gland was not enlarged. The heart was enlarged to the left with a systolic murmur over the aorta.

Case 7. A young man, aged 21, was sent to us because he had been rejected for military service. He had not noticed many symptoms but got hot rather easily, sweated freely and was anxious. For a long time he had had a «relaxed throat». The patient was a strongly-built man (height 1.75 m, weight 65 kg). The pulse was regular and even, 96 per min.; blood pressure 160/80. No ocular signs. There was a typical fine tremor of the fingers. The patient had distinct dermatographia. After he had undressed the red patches appeared on the neck and chest. The thyroid gland was symmetrically enlarged. A systolic heart murmur was audible, vanishing on exertion. Basal metabolism +37 %; blood cholesterol 2.19 ‰. Leukocytes 7,000; eosinophiles 3 %; staff cells 4 %; segmented cells 52 %; lymphocytes 32 %; monocytes 8 %.

Case 8. A fifteen-year-old girl had been suffering for 18 months from a painful sensation in the back and from shortness of breath on exertion for a year. She was easily tired, anxious and irritable, sweated considerably and blushed frequently. She could stand cold better than heat. The arms and legs were slightly bluish in colour. She had not lost weight, rather on the contrary, and had a good appetite. She suffered occasionally from palpitations. Defaecation and micturition were normal. Menstruation was excessive and the backache was worse at these times. The patient was a very broad, heavily-built girl; height 1.72 m, weight 78 kg. There was pronounced dermatography and upon undressing the arms and legs showed red patches.

The pulse was full and regular, rate 120; blood-pressure 220/120.

The eyes showed slight exophthalmia. The thyroid gland was firm and enlarged equally in all directions. Heart and lungs showed no abnormalities worth mentioning. Liver and spleen were not palpable. There was a fine tremor in the fingers.

Basal metabolism +39 %. Blood cholesterol 1.77 %; esters 0.88 %; Leucocytes 6,300, eosinophiles 2 %, segmented cells 52 %, lymphocytes 41 %; monocytes 5 %. The renal function was normal (concentration to 1.030). The pyelograms showed nothing abnormal. The sedimentation rate was 6 mm after 1 hour. The E. C. G. was normal. The blood-sugar curve after administration of 50 g glucose was normal.

Rest caused the metabolic rate to drop to normal and the blood pressure also fell to 135/75. When the patient got up the metabolic rate rose again (+33 %). The patient then received first 3×100 mg and later 2×100 mg of prominal, after which the metabolic rate decreased to +10 %. The blood pressure remained at 130/75.

Case 9. A girl aged 21 years complained of pain to the left of the heart region. She had frequent headaches above the right eye, sweated readily and could stand cold better than heat. The appetite was good and there was no loss of weight. Defaecation and micturition were normal. Ten years earlier she had suffered an affection of the kidneys with blood in the urine.

The patient was strongly-built and well-nourished (height 1.56 m; weight 60 kg). The pulse was rapid (120 per minute) and regular. Blood pressure 195/115. The thyroid gland was not enlarged.

The eyes showed no abnormalities. The heart was not enlarged; a slight systolic murmur was audible at the aorta and the aortic second sound was accentuated. The lungs, liver and spleen were normal. There was a fine tremor of the fingers.

The basal metabolism was +1 %. The renal function was normal (concentration 1.032); blood urea 350 mg per litre. Intravenous pyelograms were normal. Sedimentation rate after 1 hour 10 mm, leucocytes 11,000; eosinophile cells 1 %; staff cells 2 %; segmented cells 76 %; lymphocytes 18 %; monocytes 3 %.

The blood cholesterol was 2.35 %₁₀₀. The blood sugar curve after administration of 50 g glucose was normal. The E. C. G. showed only a negative T³ which became positive after injection of gynergen.

After the patient had taken things quietly for a few months her condition was much improved. The blood pressure had decreased to 165/90 and the pulse rate was approx. 100.

Case 10. An 18-year-old boy had been complaining for a year of pain in the top of the head. He was easily tired and disinclined for work. If he exerted himself the pain in the head became worse and he had a throbbing sensation in the temples. At first he had sweated considerably but this improved with rest. There was no loss of weight and the appetite was excellent. Micturition and defaecation were unaffected. The patient could stand cold better than heat.

The patient was a strongly-built lad, well-nourished (height 1.73 m; weight 75.1 kg). The pulse was rapid — 112 per minute — and the blood pressure fluctuated between 155/80 and 160/80. The thyroid gland showed slight symmetrical enlargement. The heart and lungs were normal. The liver was palpable (a finger breadth below the costal arch).

The basal metabolism was +29 %. The blood cholesterol was 1.45 %₁₀₀. Sedimentation rate after 1 hour 2 mm. Leukocytes 6,800; basophile cells 1 %; eosinophile cells 3 %; staff cells 1 %; segmented cells 60 %; lymphocytes 28 %; monocytes 8 %.

The E. C. G. showed a negative T^s which disappeared after administration of synergen.

The above described cases exhibit the constant recurrence of the same typical syndrome, *i. e.* tachycardia, more or less increased basal metabolism, hypertension with normal renal function and no abnormalities in the kidneys (normal pyelograms), usually a fine tremor of the fingers and frequently enlargement of the thyroid gland.

For differentiation from thyrotoxicosis the following peculiarities of this syndrome should be noted. The anamnesis showed that these patients, like sufferers from thyrotoxicosis, sweated too readily and excessively and were able to stand cold better than heat. An important difference is that the patients with this syndrome frequently complained of cold feet.

The state of nourishment is generally good and there is no loss of weight, in fact the patients are generally rather overweight (see table). In thyrotoxicosis the pulse pressure is usually high, this being, however, due rather to lowering of the diastolic than to increase of the systolic pressure. In Page's syndrome both systolic and diastolic blood pressure are high.

The patients show marked dermatography and when they are undressed numerous red patches appear on the neck and chest and sometimes even on the abdomen. The thyroid gland is either

of normal size or enlarged, but the enlargement had in most cases already been present for a considerable time before appearance of the syndrome.

We observed a typical difference as regards the cholesterol content of the blood; this is generally lowered in thyrotoxicosis, whereas in these patients it was normal or high, usually the latter (see table).

As Page had already found, operation on the thyroid gland is of no service in these cases. We administered thiouracil to some of our patients but also without the slightest success (see graph). Neither the basal metabolism nor the tachycardia could be influenced in this way. We had found successful treatment of thyrotoxicosis cases with thiouracil to be invariably followed by an increase in the cholesterol content of the blood even when this had not been below normal before treatment. In the cases described here the cholesterol level was unaffected by treatment with thiouracil.

Our cases show, further, that this syndrome may also develop in later life and may involve a much greater increase in basal metabolism than reported by Page.

As prominal is known to be a brain-stem narcotic we¹ used it on our patients giving 2—3 × 200 mg daily. Remarkable improvement soon resulted. The pulse rate dropped to normal and the basal metabolism also approached the normal value. A very striking decrease in blood pressure also occurred (see graph).

Prominal was introduced by Fenz² for the treatment of thyrotoxicosis. On closer investigation I found that some of his patients also had a high blood pressure; it appears probable that a number of Fenz's patients were actually suffering from Page's syndrome.

Hoff³ and Jores⁴ have also confirmed the beneficial effects of prominal. The improvement shown by our patients with Page's syndrome after administration of prominal is evidence that excessive irritability of the vegetative centres in the diencephalon is in fact of great significance (Page). In this connection I should like to draw attention to yet another case-history, as follows:

A woman aged 32 had complained for the past year of being easily tired. She sweated a great deal, suffered very much from the heat and had cold feet when the weather was chilly. She was

¹ van Buchem: Ned. T. voor Geneesk., 91 (1947), p. 794.

² Fenz: Wiener Arch. f. inn. Med., 30 (1937), 15, 135.

³ Hoff: Klin. Wochenschr., 16 (1937), 1305.

⁴ Jores: Klinische Endokrinologie, 1942.

nervous and flurried but seldom had headaches; difficulty in falling asleep. For the last few years she had led a very busy life. The appetite was good and micturition and defaecation were undisturbed. The patient was well-built and fairly well-nourished (height 1.66 m, weight 55.2 kg). The pulse was regular and equal, 120; blood pressure 170/95. A small hard nodule was detected in the right lobe of the thyroid gland. The heart was not enlarged. A slight systolic murmur was heard over the aorta with accentuated aortic second sound.

The basal metabolism was +82 %. The blood cholesterol was 1.4 ‰. Leucocytes 2,200, eosinophiles 3 %; staff and segmented cells 63 %; lymphocytes 29 %; monocytes 3 %. Sedimentation rate 8 mm after 1 hour. The renal function was good; the E. C. G. showed nothing abnormal.

After treatment consisting of rest and administration of prominal the blood pressure gradually became normal (140/90). The basal metabolism first decreased gradually to 39 % but then proceeded to fluctuate widely (+50—+60 %). A remarkable fact is that the patient's weight greatly increased, from 55.2 to 66 kg. The x-ray photo of the skull was normal, in particular there was no hyperostosis frontalis and the sella turcica was normal.

A change also appeared in the patient's appearance, the face assuming a tense expression.

The cerebrospinal fluid showed nothing abnormal (Pandy and Nonne tests negative; number of cells 3/3; lymphocyte, gold-sol and syphilis reactions negative). A fact worthy of note is that the patient's father had suffered from paralysis agitans.

The question with which we are faced here is: What is responsible for the increased basal metabolism and the tachycardia? Are these conditions brought about through the intermediacy of the thyroid gland?

Brouwer¹ describes the case of a patient showing the clinical picture of exophthalmic goiter in connection with a cerebral meningioma which exerted pressure on the hypophysis and hypothalamus. The signs of exophthalmic goiter were of recent origin. The thyroid gland showed the characteristic histological findings of the Basedow's disease. In this case it is possible that the hyperthyroidism was caused either by irritation of the hypophysis (with production of thyrotropic hormone) or by irritation of the autonomic centres from which the thyroid gland is innervated.

¹ Brouwer; Ned. T. voor geneesk. 90 (1946), 840.

In my opinion the pathogenesis of the signs observed in patients with Page's syndrome is different from that mentioned in the foregoing paragraph. It is well-known that treatment with thiouracil inhibits the formation of thyroxin and thus leads to disappearance of the hyperthyroid phenomena. With Page's syndrome we found thiouracil treatment to be without effect. If there were in fact a hyperfunctioning of the thyroid gland due to irritation of the diencephalic centres, then thiouracil would be expected to show some effect. It should also be noted that operative treatment has proved useless in such cases. The thyroid gland of case 7, who has been operated, showed the histological findings of a diffuse colloid goiter. In view of these facts it is also no matter for surprise that Bruins Slot¹ was unable to show increase of thyrotropic hormone in the blood in two out of three cases of what he termed juvenile hypertension with increased basal metabolism.

Table.

Sexe	Age	Length m.	Weight (kg)	Pulse frequency	Basal metabolism	Blood pressure	Choleste- rol. blood
♀	61	1.53	58 kg	144	+ 62 %	210/105	1.88 % ₁₀₀
♀	49	1.70	83.8 »	88	+ 38 %	215/105	2.4 »
♀	56	1.66	53.5 »	104	+ 45 %	205/130	2.61 »
♀	55			96	+ 39 %	230/130	3 »
♀	59			124	+ 31 %	235/150	2.81 »
♀	61			80	+ 54 %	235/130	2.96 »
♀	21	1.75	65 »	96	+ 37 %	160/80	2.19 »
♀	15	1.72	78 »	120	+ 39 %	220/120	1.77 »
♀	21	1.56	60 »	120	+ 1 %	195/115	2.35 »
♀	18	1.73	75.1 »	112	+ 29 %	160/80	1.45 »
♀	32	1.66	55.2 »	120	+ 82 %	170/95	1.45 »
			↓ 66 »				

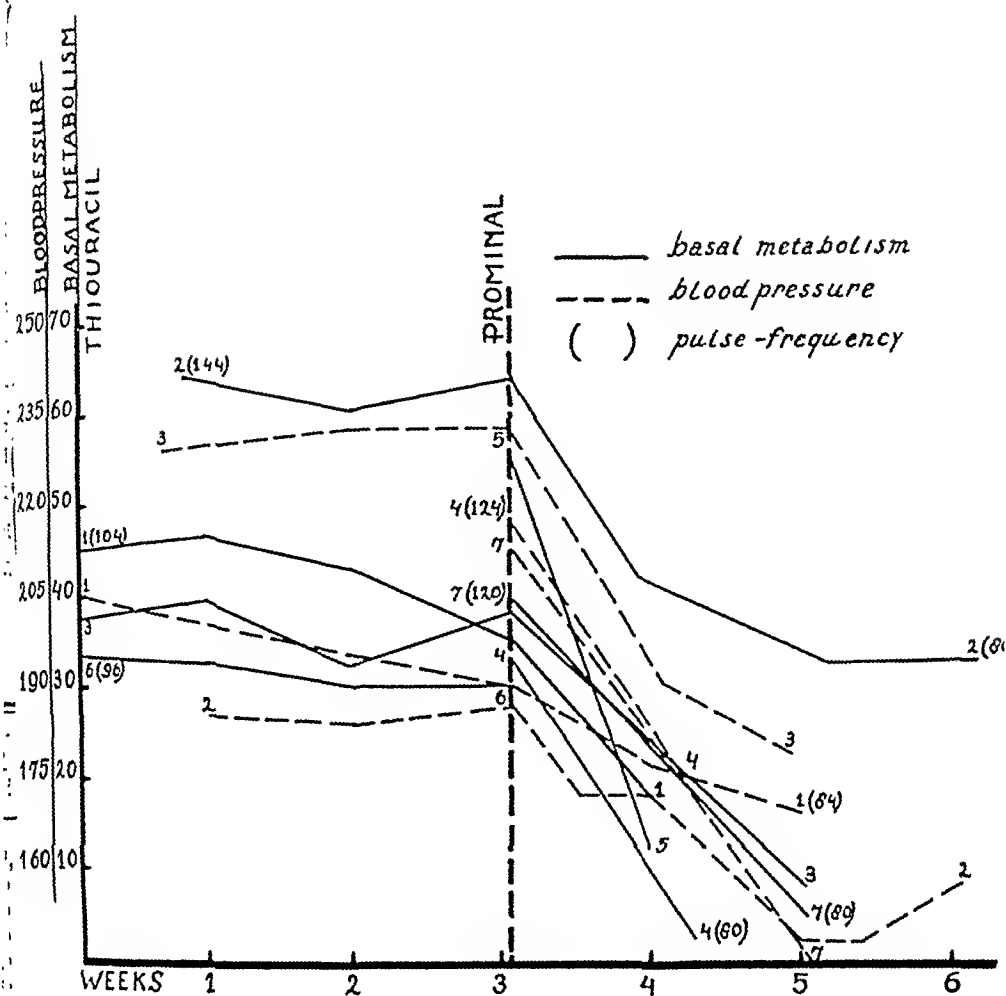
Summary.

The author gives 10 case-histories of the hypertensive diencephalic syndrome, described by Page.

This syndrome may involve a far greater increase in basal metabolism than reported by Page.

Frequently the diagnosis of thyrotoxicosis is wrongly made. As a rule the author found by these patients a normal or high

¹ Bruins Slot; Ned. T. voor Geneesk., 86 (1942), 1184.



cholesterol content of the blood instead of a lowered one generally found with thyrotoxicosis. In these cases neither an operation of the thyroid gland nor the administration of thiouracil is of any service whatever. Prominal, being known as a brain stem narcoticum, we tried it on our patients. Remarkable improvement was often resulted. The increased basal metabolism, the tachycardia and most of the other symptoms of this syndrome are not brought about by the intermediary of the thyroid gland.

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Cushing's Syndrome in a 55 Years Old Man.

Report of a Case with Decreased Serum Protein Values
and Pathologic Changes of the Adrenal Cortical Cells.

By

CHR. JUEL BJERKELUND and OLAV TORGERSEN,

(Submitted for publication September 22, 1947.)

Since Cushing's classical description of the basophile adenomas of the pituitary body and their clinical manifestations in 1932, an extensive literature has accumulated all over the world on the syndrome associated with his name. In Scandinavia cases have been reported by Wicth-Pedersen, Ingvarsson & Lindberg, Josephson & Bergstrand, Rischel, Per Hanssen, V. Fürst jun., Clemmesen, Kveim, Bentsen, Flensburg, Höher, Borberg, Quist-Hanssen, Petersen, P. Hansen, Ramvad & Thorborg, Mørch-Christensen & Poulsen, Aubert and Jerre. — Special studies on the pathology have been carried out by Gellerstedt, Lundquist and Mellgren, and with regard to the pathological physiology and therapy, by Luft.

Cushing considered the basophile adenoma of the pituitary to be the cause of the syndrome. He also, however, attributed some importance to other glands, especially the adrenals. — Later a series of cases have been reported, in which no pituitary adenoma was found. In a number of cases a tumor of one adrenal cortex or a hyperplasia of both cortices was present, or in rare instances a carcinoma of the thymus. Regardless of the absence or presence of a pituitary adenoma, the »hyaline» changes in the basophiles, described by Crooke, seems to be the most constant pathologic finding.

Concerning the terminology, the suggestion made by Kessel is gradually being adopted. The term »Cushing's disease» is reserved for those cases in which a basophile adenoma of the pituitary is present. The syndrome as a whole, whatever the causation, is referred to as »Cushing's syndrome».

The many questions still concerned with the clinical and pathologic picture of the syndrome may justify further case reports, especially in instances differing from the main group of patients described in the literature. The following somewhat unusual case may possibly be of interest.

Case report: Labourer 55 years old. Admitted to Kristiansand Hospital, Medical Dept. Nov. 2. 1946. Wife and 3 children healthy. No known cases of metabolic disorders or tuberculosis in the family. In 1919 he had influenza. In 1939 ulcer rodens, localized to the right temple, cured after radium treatment. Otherwise previously in very good health. — The present disease was noticed by the patient in July 1946. He began to put on weight, his abdomen, especially, growing stout and heavy. After a while he could not get into his trousers, his tailor had to make him another pair. Simultaneously he noticed increasing adiposity of his face, which became great, round and intensely red in colour. He also suffered from burning and sharp pains in the skin of his face and over the neck, especially when bending forwards, during his work. His friends could scarcely recognize him. Many of them asked him if he had mumps, or what on earth he lived on since he became so stout and ruddy-cheeked. Little by little he encountered difficulties in doing his job. He complained of pains in the back and stiffness due to the size of his abdomen. Gradually he lost interest in everything around him, developing increasing dullness and fatigue. He could rest seated and apathetic for hours. Repeatedly he fell asleep immediately he sat down in a chair. The last month before his admittance a marked disposition for sweating. Simultaneously he complained of short breath on effort. Last 2 weeks before admittance increasing edema of the lower part of the legs combined with pain when walking. Previously no ankle edema. He also noticed intermittent swelling and edema of hands and wrists. One week before admittance unfit to work. Marked fatigue, dullness and loss of initiative. His family, being alarmed about his state, called the doctor who sent him to hospital. — Since the beginning of the disease remarkably increased appetite. Had been eating unnaturally much. Could never be satisfied. Increased in weight by 18 kg in the course of 3—4 months. No thirst, no polydipsia. Urination and bowels normal. Sexual function markedly decreased the last 6—8 months, with loss of libido. Previously regular and normal sexual life.

Status presens: Height 178 cm. Weight: 88 kg. Adiposity chiefly localized to face, neck and abdomen. (Figs. 1 and 2.) Extremities relatively thin (except for the edemas). Face swollen, rounded, dark reddish-purple in colour. Skin thin, tense and shiny. The superficial

veins markedly teleangiectatic, forming a distinct bluish plexus beneath the skin. The subcutaneous tissue of the face and over the neck considerably thickened. Slight kyphosis of the superior part of the thoracic spine. General condition markedly reduced. Voice hoarse. Breathlessness on effort. Somewhat indolent, but giving plain answers to questions. Complains of burning pains in the skin localized to face and neck. Pulse: 76, reg. BP: 170/100. Controls: Nov. 11th and Nov. 17th.: 125/95 and 145/100. Temp. normal. On the lower lip a fissure-like, scarcely infiltrated wound is noticed. Heavy edema of the lower extremities extending up to the gluteal region and of the sacral region. The skin of the trunk and the limbs light purplish in colour somewhat mottled over the abdomen and the flanks. No striae distensae. Heart and lungs: Nothing abnormal. Abdomen: Massive adiposity of the subcutaneous tissue. Pubic hairs relatively scarce. — Otherwise nothing remarkable at the clinical examination. — The first two days in the hospital his diet consisted of 800 cc milk a day (Karell-regime). The following period he had a diet with restricted chloride intake. His edema decreased a little the first days, later his condition was unchanged. Most of the day he was lying dull and almost immovable in his bed, but he willingly answered questions from the doctors. His general condition, however, gradually deteriorated. He suffered heavily from sweating and complained of thirst. From Nov. 15th his edema again increased and edema also developed in the scrotum and of the hands and lower arms. He began to cough and had a sticky, yellowish expectorate. From Nov. 17th numerous tiny, round, clear vesicles (sudamina) were noticed on his shoulders and the upper part of his chest. Nov. 23rd: Marked drowsiness and fatigue. Over the top of his left lung physical examination revealed numerous sibilant and moist rales. Weight increased to 92 kg (edema). Decreasing appetite. — He was afebrile until Nov. 25th when his temperature suddenly rose to 39.5° C. and the patient was markedly failing, suffering from dyspnea, cough and expectoration. Respiration frequent. The following days febrile, temperature varying between 40 and 40.5° C. Signs and symptoms of a croupous pneumonia. He died Nov. 29th 1946.

Roentgenologic examinations:

Teleradiogram (Nov. 4th -46): Size and shape of the heart normal. Width of the heart: 15 cm. Width of the chest: 35 cm. — In the left pulmonary field, at the level of the first intercostal space anteriorly, a number of very fine, uneven, indistinctly outlined shadows are noticed, localized to an area 6 × 2.5 cm in size.

Control (Nov. 21st -46): Compared with the roentgenogram dated Nov. 4th -46, a very considerable progression of the pathologic process in the top of the left lung can be seen. The process is now involving the entire superior lobe and is extending distally to the 7th costa counted on the posterior chest wall. Streaks downwards to the left hilus are noticed. Left hilar shadow moved somewhat in the lateral direction.

Roentgenogram of the head (Nov. 8th -46): Normal bone structure and normal calcification. Pineal body calcified. Sella turcica somewhat shallow. (Length: 14 mm, depth 6.5 mm).



Fig. 1. The patient 1½ year before onset of symptoms.



Fig. 2. The patient 1 week after his admittance.

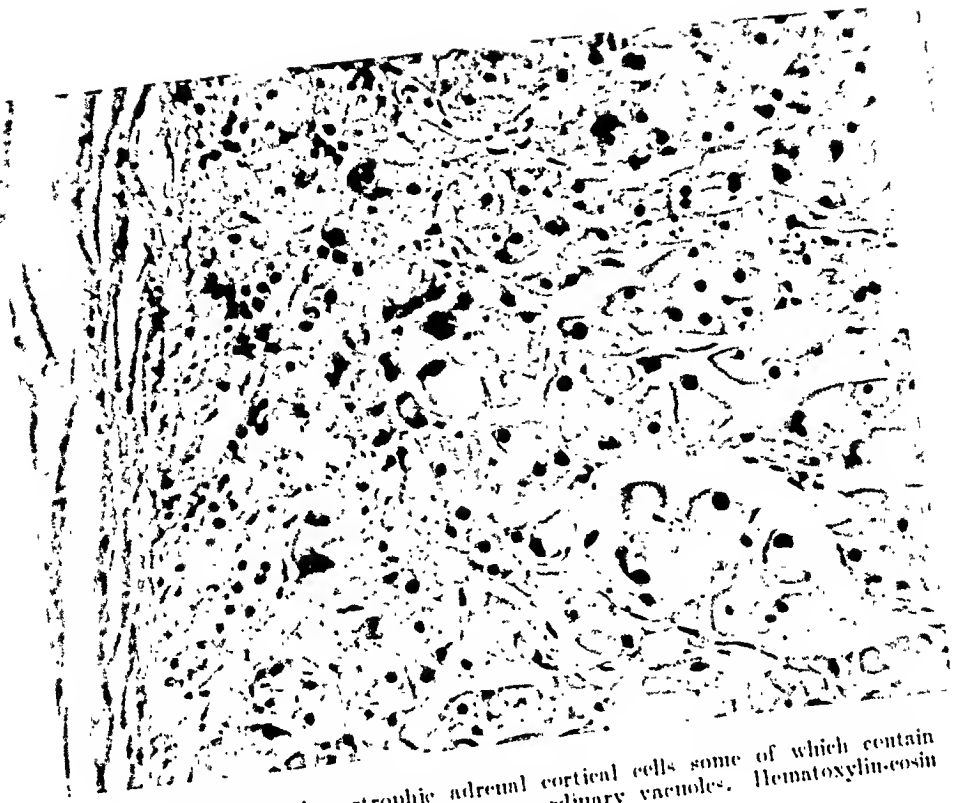


Fig. 7. Markedly hypertrophic adrenal cortical cells some of which contain light areas in their cytoplasm, but no ordinary vacuoles. Hematoxylin-eosin ($\times 200$).

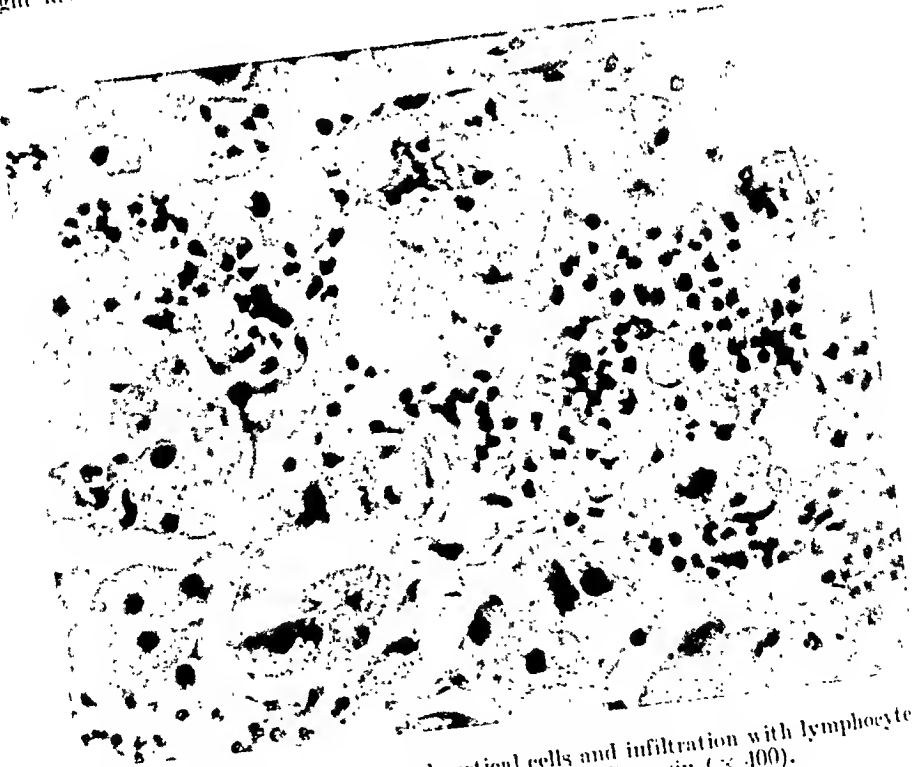


Fig. 8. Local necrosis of adrenal cortical cells and infiltration with lymphocytes and polymorphonuclears. Hematoxylin-eosin ($\times 400$).

Roentgenograms of the abdomen and of the left renal region (repeated examinations): Corresponding to the superior pole of the left kidney an oval, faint shadow (soft tissue) can be seen, regularly outlined and about 7×5 cm in size.

This shadow was supposed to be a tumor of the left adrenal cortex and the possibility of surgical intervention was discussed with the chief surgeon of the hospital. The patient's general condition did, however, not permit immediate surgical treatment. One decided initially to try irradiation of the pituitary body and the «adrenal tumor» and treat his edema with diuretica.

Intravenous urographia (Nov. 13th and Nov. 19th): No pathologic changes of the calyces, pelvis or urether on either side.

Roentgenogram of the spine (Nov. 14th): Marked spondylotic changes of the lumbar spine. Schmorl's herniae. Osteoporosis. Very pronounced calcification of the distal part of the aorta.

Eye: Visual fields normal outlines. Ophthalmoscopy: Nothing particular.

Oto-laryngologic examination: Nose: Atrophic rhinitis with crust formation. Ears: Sequelae otit. med. bilat. Hearing decreased on both sides to 1 m whispering voice. Larynx: Nothing particular. Pharynx: Normal. Tongue thick and rigid.

Laboratory findings: Urine: Albumen, Blood, Pus, Sugar, Ehrlich and Gries all negative. Urobilin (Schlesinger): $+ 1/40$.

Nov. 4th: SR: 6 mm/1 hour. R. bl. corp. 5.32 mill. Hgb. 95 %. Colour index: 0.84. Haematokrit: 47 %. Reticulocytes: 0.2 %. Average diam. of r. bl. corp. (Halometry): 7.2 my. Leucocytes: 11400. Diff. count: Staff 5 %, Segmented 76 %, Eosinophiles 7 %. Lymphocytes 8 %. Monocytes: 4 %. Sternal marrow as well as blood smear showed toxic granulation of the neutrophiles. Otherwise no comment.

Nov. 26th: R. bl. corp. 4.29 mill. Hgb. 80 %. Colour index: 0.88. Haematokrit: 39 %. Reticulocytes: 0.5 %. Leucocytes: 9200. Diff. count: Staff 37 %, Segmented 48 %, Lymphocytes 15 %.

Nov. 11th: WR, Icterus index, Takata, Bleeding time, Clotting time, Capillary resistance (Göthlin): Nothing particular.

Electrocardiogram: Nov. 4th: Normal. Nov. 25th: Fibrillo-flutter.

Blood sugar fasting: Nov. 8th: 142 mg %, Nov. 15: 154 mg %.

Glucose tolerance test (1 g glucose per kg body weight):

Time:	0 H.	$1\frac{1}{2}$ H.	1 H.	$1\frac{1}{2}$ H.	2 H.s
Blood sugar:	150 mg %	225 mg %	290 mg %	300 mg %	295 mg %
Urine sugar:	0		1.8 %	2 %	2 %

Standard metabolic rate: Nov. 9th: 128 %. Nov. 14th: 103 %.

Serum proteins (after Bing): Nov. 6th: 4.5 %. Nov. 18th: 5.5 %.

Serum proteins (fractionated): Nov. 6th: Alb. 3.45 %. Glob. 1.69 %.

Total proteins: 5.14 %. Alb./Glob.: 2.04. Non-protein N: 28 mg %.

Nov. 18th: Alb. 3.45 %. Glob. 2.74 %. Total proteins: 6.19 %.

Alb./Glob.: 1.26. Non-protein N: 12.1 mg %.

Nov. 12th: Total base: 155.6 m. eqv. per l. Chlorides: 90 m eqv. per l.

Calcium: 9.7 mg %. (Nov. 18th Calcium 9.4 mg %.) Phosphor: 3.3 mg %.

Phosphatase: 8.1 units (alk. Bodansky). *Cholesterol*: 235 mg %.

Hormon titration (urine): Gonadotropin: F. S. H. < 33 M. U. per l. L. H. < 33 M. U. per l. 17-ketosteroids: 21 mg/24 hours (determined as dehydroandrosteroneacetate).

Autopsy (performed 9 hours post mortem):.

The body was that of an elderly man with the external characteristics of Cushing's syndrome (except for the striae). The upper lobe of the left lung was consolidated, resembling the state of grey hepatization. In the left lower lobe and in all the lobes of the right lung were a number of small, greyish nodules with necrotic centers. At the superior pole of the left kidney a mandarin-sized, solitary cyst was found, greatly distended with fluid. The adrenals weighed 18 g (traces of fat tissue adhering to the capsule). The cut surface appeared normal and no adenomas could be found. Examination of the other organs, especially the pituitary gland, the thyroid and the testicles revealed no abnormalities. No thymus could be found. The autopsy was carried out under unfavorable conditions and systematic weighing of the organs could not be made.

Histological examination:

Lungs: The alveoles were partly atelectatic, partly distended and edematous. In large areas massive caseous necrosis was noticed, surrounded by scanty epithelioid cells, lymphocytes and macrophages. Staining after Hallberg revealed numerous acid-fast bacilli.

Hypophysis: Thirty slides were stained either with hematoxylin and eosin or with van Gieson's stain, Mallory-azan or after Crooke-Russell. The posterior lobe had a small pea-sized defect, partly filled with cells of the anterior lobe type. Some of these were frankly basophilic, very few eosinophilic or belonging to the transitional forms. The rest were small and rather of the chromophobe type. The anterior lobe had a fairly homogenous structure without any sign of adenoma. The chromophobe type of cells were possibly somewhat reduced in number, but the cells present were normal. The basophilic cells were found in normal number, partly arranged in small groups. A minor portion of the basophiles had normal size, shape and granulations, but most of them showed the typical »hyaline» changes described by Crooke. These changes could be seen also in the hematoxylin-eosin preparations (Fig. 3). The eosinophiles were numerous, possibly somewhat augmented. Many of these cells were normal. Some contained light, slight basophilic inclusions in their cytoplasm. In some places atrophic or degenerated cells with light eosinophilic cytoplasm could be seen. These were partly arranged in acini, surrounding a granular mass of »inspissated» colloid (Fig. 4). The stroma and blood vessels of the anterior lobe were normal. Staining for tubercle bacilli gave negative result.

Thyroid: The thyroid gland contained numerous large alveoli with a low, regular, squamous epithelium. The colloid was mainly basophilic, without vacuoles. The stroma was slightly augmented, partly fibrous, partly edematous. No lymphoid tissue, nor leucocytic infiltration was found.

Adrenals: The cortex was considerably thickened (about twice the

normal). The cortical epithelium was somewhat autolysed, but there seemed to be a considerable edema as well. The arrangement of the cortical cells was irregular. In small well defined areas, normal or slightly degenerated cortical cells with the usual vacuolated cytoplasm were noticed (Fig. 5). In sudan-stained sections, these cells showed large amounts of fat, some of which was doubly refractile. Most cortical cells, however, contained only very scarce amounts of finely distributed fat droplets. In hematoxylin-eosin preparations some of these cells were found to be of the usual size and form, slightly basophilic and not vacuolated. In Malloryazan preparations, the cytoplasm of these cells was slightly brownish, finely granulated. Apart from this type of cell, which is commonly found in patients with lowered general condition, there were numerous other cells, differing from these in having round or irregular, finely granulated, lighter areas in their cytoplasm (Fig. 6). These areas contained only very scarce amounts of fatty substances, apparently not more than the surrounding dark cytoplasm. In Mallory-azan preparations, the granulated cytoplasm in these areas had a light blue colour, sharply contrasted to the surrounding brownish cytoplasm. The light areas were most commonly found near the nucleus, in the part of the cell most rich in cytoplasm. The size of the light areas varied from that of a nucleus to large areas, leaving only a thin border of dark cytoplasm at the periphery of the cell (Fig. 6). Irrespective of the cellular structure, a great amount of the cortical cells were markedly hypertrophic (Fig. 7). In several parts of the cortex, patches of necrotic tissue were noticed, considerably infiltrated with lymphocytes and polymorphonuclears (Fig. 8). No acid-fast bacilli could be detected in these areas. In some places, small, fibrotic areas were found. The cortical capillaries were partly dilated. In the zona reticularis one could see a few small hemorrhages. The adrenal marrow was found to be normal in the sections examined.

Pancreas: The acini were normal or slightly atrophic and there was a marked patchy or diffuse fibrosis. The islets of Langerhans were mainly well preserved. In Mallory-azan preparations, relatively few B-cells were found. Some of these contained very faintly stained granules and these cells, as well as some of the A-cells, were often vacuolated.

Testicles: The seminiferous tubules were built up of a considerable number of spermatogonies, but the amount of primary and secondary spermatocytes was very much reduced. No spermatids were detected. The connective tissue was edematous. A few interstitial cells of Leydig were found. Some of these had small amounts of light, brownish pigment in their cytoplasm.

Liver: The liver parenchyma showed an enormous accumulation of fat. The central parts of the lobuli were most heavily affected. The bile ducts and blood vessels were mainly normal.

Kidneys: The renal capsule was normal. Most glomeruli had the usual structure, without any signs of endothelial or epithelial proliferation. In some glomeruli there was a diffuse thickening of the basement membrane resembling the intercapillary glomerulosclerosis described

by Kimmelstiel and Wilson (1936). The tubuli were autolysed, but there was no sign of severe damage. The connective tissue was slightly augmented, but without any sign of active inflammation. The arterioles were thinned, without intimal hyperplasia or sclerosis. The archiform arteries were slightly sclerotic. The veins were distended. The juxtaglomerular apparatus showed no conspicuous changes. A Sudan-stained section revealed no fatty substances.

Summary: In a previously healthy man, 55 years old, the typical picture of Cushing's syndrome developed rapidly in the course of 3–4 months. The chief signs and symptoms were the following: Markedly increased appetite. Rapidly increasing body weight. Obesity localized to face, neck and abdomen. Typical «full moon face», dark purplish in colour, with marked teleangiectatic superficial veins. Acrocyanosis of the skin. Increasing dullness and loss of interest. Nareolepsia. Loss of libido. Slight hypertension. Osteoporosis and kyphosis of the spine. Increased fasting blood sugar and decreased glucose tolerance. Increased blood cholesterol value. Total base slightly increased. Serum chlorides slightly decreased. Phosphatase somewhat increased. Distinctly decreased serum protein values. Great edema. General condition markedly reduced. During his stay gradually falling off. After he had been afebrile the first 3 weeks, his temperature suddenly rose to about 40° C and a rapidly developing acute pulmonary tuberculosis ended the life of the exhausted patient in the course of less than a week. Post mortem examination revealed the following results:

1) Acute caseous tuberculosis of the left lung. 2) Partial degranulation and «hyalinization» of the basophile cells of the anterior pituitary (Crooke's changes). Degenerative changes in some of the eosinophile cells. Infiltration of cells of the anterior lobe type in the posterior lobe of the pituitary. 3) Considerably thickened adrenal cortex. Structural changes in the cortical cells. Patchy acute necroses and slight fibrosis of the cortex. 4) Moderate fibrosis of the pancreas. Possible diminution of the amount of B-cells in the islets of Langerhans. 5) Retrogressive changes in the testicles. 6) Severe fatty degeneration of the liver. 7) Inter-capillary glomerulosclerosis (?) in the kidneys. Solitary cyst in the left kidney.

Discussion.

There can be no doubt about the diagnosis in this case. The symptoms and signs were typically those of Cushing's syndrome (except for the striae) and the diagnosis is further supported by the results of the post mortem examinations.

As to the clinical picture the following points deserve special attention:

The age of the patient, 55 years, is rather uncommon. Among 155 cases published up to 1940 (Malaguzzi-Valeri) only 4 patients were over 50 years old.

The course of the disease was unusually rapid (4 months). The average duration of life in Cushing's syndrome from the onset of the symptoms is 5 years (Moore). Considering that a number of these patients die within a shorter time from a malignant tumor of the adrenal cortex, the mean duration of life in the non-tumor group is presumably even longer. Most patients die of infections due to the decreased resistance in this endocrine disorder. In our patient an acute pulmonary tuberculosis, developing rapidly in the terminal stage, ended the patient's life. The symptoms were those of an acute croupous pneumonia. We wish to stress, however, the rapid and malignant course of the Cushing's syndrome itself in the present case. It must be pointed out in this connection that his SR was normal (Nov. 5th) and that he was afebrile, showing no symptoms of infection until the last few days. He was then already extremely reduced from his endocrine disorder, and most likely would have died within short without any infection.

The serum protein values were distinctly decreased. Thus shortly after his admittance the following values were found: Albumen 3.45 %, globuline 1.69 %, total protein 5.14 % (after Bing 4.5 %). The albumen values were found unchanged two weeks later, whereas the globuline values had increased to 2.74 %, possibly as a consequence of the patient's infection. The patient's edema can most likely be considered as a result of these low serum protein values. This opinion is further supported by the fact that clinical, roentgenologic and electrocardiographic examination of the heart revealed nothing abnormal, and only a slight hypertension was present.

Determination of the serum protein values are remarkably infrequently carried out in the previously reported cases. Thus in the monographs by Malaguzzi Valeri (1940) and Luft (1944) such examinations have not been mentioned. On the other hand it is pointed out by Albright, Parson and Bloomberg (1941) that there exists in Cushing's syndrome a negative nitrogen balance and a protein shortage from which results weak muscles, thin skin and osteoporosis. This negative nitrogen balance is believed to result from a hypergluconeogenesis, which in turn is regarded as the main basis of the disturbance of carbohydrate metabolism in these cases. Luft, in a personal communication (1947), reports that he has now two cases of Cushing's syndrome with low serum protein values. He considers this to be due to an increased function of the adrenal cortex, resulting in a transformation of protein to glucose.

As to the pathology, the following findings have to be pointed out.

The hypophysis: In the posterior lobe two small areas infiltrated with cells of the anterior lobe type, mainly basophiles, were found. These areas, however, were indistinctly outlined and cannot be characterized as adenomas. In the anterior lobe a number of the basophiles showed typical Crooke-changes (Fig. 3). The sections further revealed degenerative changes in a number of the eosinophiles. Some of these were occasionally seen to form part of an alveole containing frankly abnormal »colloid» (Fig. 4).

The absense of a basophile pituitary adenoma can no longer be regarded as uncommon in Cushing's syndrome. In 87 cases collected from the literature, Malaguzzi-Valeri (1940) found a basophile adenoma present in only 49 patients. On the other hand, the changes in the basophiles described by Crooke (1935) have been largely confirmed by a number of investigators (Gellerstedt, Mellgren, Albright a. o.). Peculiarly small attention has been paid to the eosinophiles. Horneck (1936) described an eosinophile adenoma in a case of Cushing's syndrome. A similar observation was made by Ramvad and Thorborg (1942). The last named authors stress, however, that no pathologic changes could be detected in the eosinophile cells.

The adrenals were markedly enlarged, the cortical width being about twice the normal. The enlargement mainly seemed to be called forth by a hyperplasia of the cortical cells. A considerable number of cells, however, were frankly hypertrophic. Most cells had a dark, homogeneous or finely granulated cytoplasm in which pale areas containing granular masses were noticed (Figs. 6 and 7). In addition scattered foci of necrosis with infiltration of polymorphonuclear leucocytes were present (Fig. 8). The sections only occasionally revealed small islands of cells which had the appearance of nearly normal adrenal cortical cells (Fig. 5). These cells contained a fairly normal amount of fatty substances, while the cortical lipoids elsewhere were considerably reduced.

The significance of the adrenal cortex for the Cushing-syndrome has been the subject of much discussion. According to Albright (Harvey Lectures 1942—43) a patient with Cushing's syndrome may at autopsy present either a tumor of one adrenal cortex or hyperplasia of both adrenal cortices. In cases where the adrenal cortices have been found normal, he questions either the diagnosis, or the interpretation of the adrenal histology. In the present case marked hypertrophic and hyperplastic changes were

found. It must be emphasized, however, that nearly all the cortical cells showed distinct pathologic changes. No conclusion can be drawn as to the function of these cells. On the other hand the occurrence of scattered necrotic foci in the adrenal cortex must be underlined.

One can, however, hardly believe, that the tuberculous infection in the present case can be responsible, in one way or another, for the development of Cushing's syndrome. In the opinion of the authors, this infection must presumably be regarded as an accidental complication, resulting from the decreased resistance at the terminal stage of the endocrine disorder.

Summary.

A report is given on Cushing's syndrome in a previously healthy labourer, 55 years old. The signs and symptoms were typically those of Cushing's syndrome, except for the striae. In addition distinctly decreased serum protein values were found, resulting in heavy edema. The endocrine disorder had a malignant course and the general condition rapidly deteriorated. In the terminal stage, about 4 months after the onset of the symptoms, an acute pulmonary tuberculosis ended the life of the exhausted patient in the course of a few days. Post mortem examination revealed the following results: 1) Acute caseous tuberculosis of the left lung. 2) Partial degranulation and «hyalinization» of the basophile cells of the anterior pituitary (Crooke's changes). Degenerative changes in some of the eosinophile cells. Infiltration of cells of the anterior lobe type in the posterior lobe of the pituitary. 3) Considerably thickened adrenal cortex. Structural changes in the cortical cells. Patchy acute necroses and slight fibrosis of the cortex. 4) Moderate fibrosis of the pancreas. Possibly diminution of the amount of B-cells in the islets of Langerhans. 5) Retrogressive changes in the testicles. 6) Enormous accumulation of fat in the liver parenchyma. 7) Interapillary glomerulosclerosis(?) in the kidneys. Solitary cyst in the left kidney. The rapid and malignant course of Cushing's syndrome in the present case is underlined and the decreased serum protein values in connection with this syndrome is discussed. As to the histologic findings special stress is laid upon the interesting structural changes in the adrenal cortical cells. No conclusions can be drawn as to the function of

these cells. The patients tuberculous infection is regarded as an accidental complication, resulting from the decreased resistance at the terminal stage of the endocrine disorder.

Literature.

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